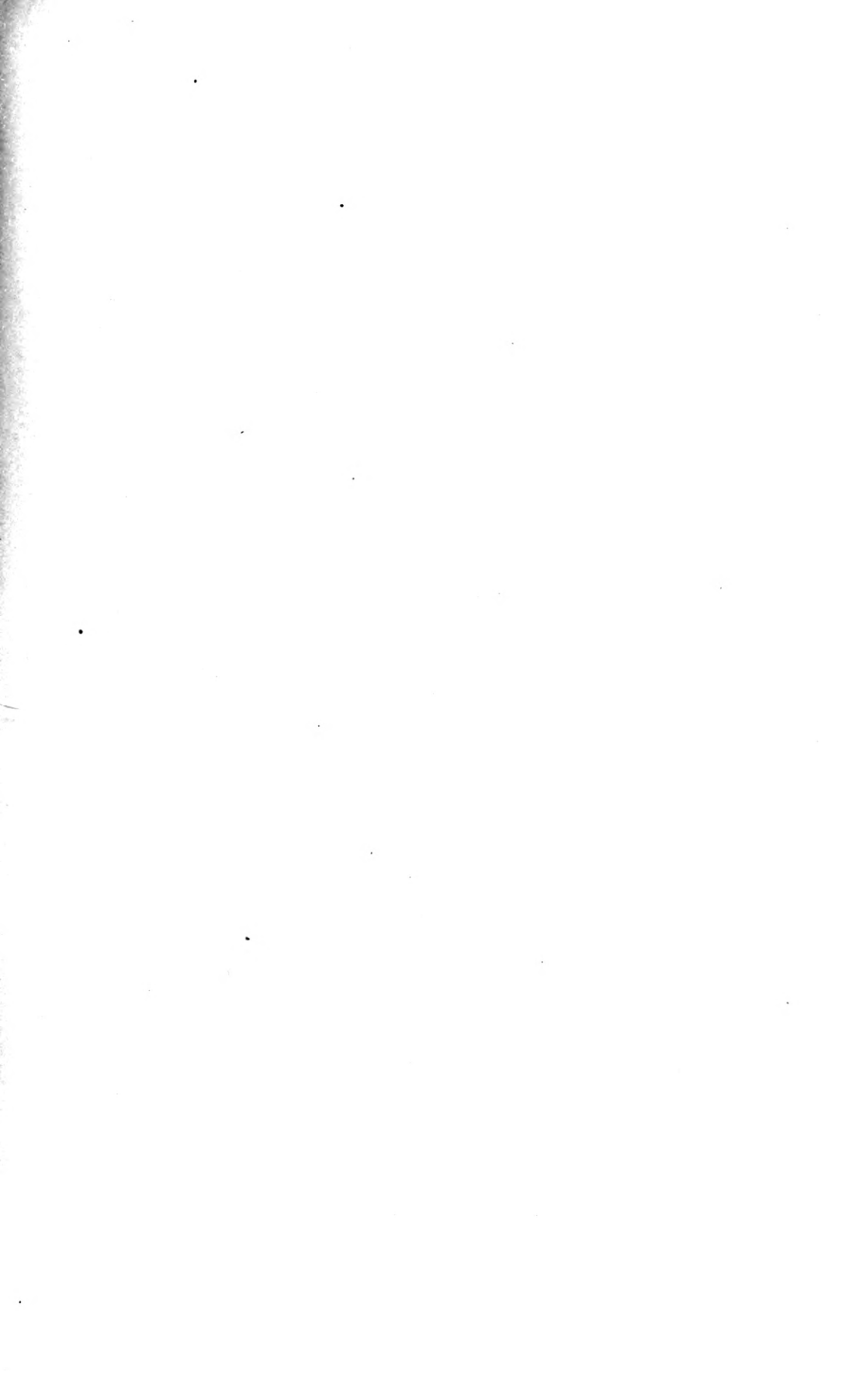


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THE NATURE OF THE PLANTAR REFLEX IN EARLY LIFE AND THE CAUSES OF ITS VARIATIONS *

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INTRODUCTORY AND HISTORICAL

In 1898 Babinski¹ called attention to the plantar reflex as a diagnostic sign in lesions of the pyramidal tracts of the spinal cord. The reflex which he called *le phénomène des orteils* consists, as is now so well known, of the plantar flexion of the big toe consequent on the tickling of the inner border of the sole of the foot. This is the normal response. When the pyramidal tracts are diseased in any part of their course, the same stimulus applied to the sole of the foot results in a dorsiflexion instead of a plantar flexion of the toe. Since then this peculiarity of the toe reflex in organic lesions of the pyramidal tract has become known as Babinski's sign or the Babinski phenomenon, and has been a subject of investigation by many observers all over the world, including Buzzard,² Collier,³ Cohn,⁴ Crocq,⁵ Cestan and Le Sourd,⁶ Van Epps,⁷ Van Gehuchten,⁸ Glorieux,⁹ Guidiceandrea,¹⁰

* Received for publication Aug. 13, 1921.

* Thesis approved for the degree of Doctor of Medicine in the University of London.

1. Babinski, J.: Du phénomène des orteils et de sa valeur semiologique. *Semaine méd.* 321, 1898; Sur la transformation du régime des réflexes cutanés, etc., *Rev. neurol.* 58, 1904.

2. Buzzard, T.: On the differential diagnosis of insular sclerosis from hysteria, *B. M. J.* 1:1077, 1899.

3. Collier, J.: An Investigation of the Plantar Reflex, etc., *Brain* 22:71, 1899.

4. Cohn, M.: Ueber die Bed. der Zehenreflex, *Neurol. Centralbl.* 18:580, 1899.

5. Crocq, J.: Die Reflexe Mit Rücksicht auf die Lebensversicherung, *Wien. med. Wchnschr.* 52: Nos. 17-25, 1902.

6. Cestan and Le Sourd: Contribution a l'étude du phénomène des orteils, *Gaz. d. hôp.* 1249, 1899.

7. Epps, C. Van: The Babinski reflex, *J. Nerv. & Ment. Dis.* 214, 1901.

8. Van Gehuchten: Quoted by Passini.²¹

9. Glorieux: Quoted by Passini.²¹

10. Guidiceandrea: Quoted by Passini.²¹

Kalischer,¹¹ König,¹² Munch-Petersen,¹³ Okada,¹⁴ Schüler,¹⁵ Schneider,¹⁶ Yoshimura¹⁷ and many others. The various findings are not in agreement. Thus, while all French and British observers, as well as most investigators of other countries, confirm Babinski's statement, other neuropathologists (Cohn, Kornilow,¹⁸ Schüler, Tumpowski,¹⁹ and others) either consider the test unreliable, or attach no diagnostic significance to it. Kornilow says:

Although Babinski's sign often occurs in the presence of functional disturbance of the pyramidal tract, there are also cases of disease of the pyramidal tracts without the presence of Babinski's sign. On the other hand, cases have been observed in which there was an undoubted Babinski's sign, and which at the necropsy revealed perfectly normal pyramidal tracts. The differential diagnostic significance of the Babinski phenomenon for the purpose of distinguishing organic from hysterical hemiplegias is not pathognomonic. There are cases of hysteria in which the Babinski sign is present.

Chodz'ko²⁰ criticizes the observations of Babinski's opponents as inexact and as probably due to defective methods of observation.

While, therefore, there is no absolute unanimity on the matter, the balance of evidence is preponderatingly, one might even say, overwhelmingly in favor of the diagnostic significance of the Babinski phenomenon.

Passini²¹ confirms Babinski's statement in the case of children suffering with pyramidal lesions (cerebral diplegia and monoplegia, congenital hydrocephalus with spastic paresis of the lower extremities, spinal diseases, e. g., compression myelitis due to spinal caries).

Babinski having found this peculiarity of the toe reflex in pyramidal disease of the spinal cord, expected a priori to find similar dorsiflexion of the big toe as a physiologic phenomenon in early infancy, at a time

11. Kalischer, O.: Ueber den Normalen und Pathologischen Zehenreflex, Virchows Arch. f. path. Anat. 1899.

12. König, W.: Ueber die bei Reizung der Fusssohle zu beobachtenden Reflexerscheinungen, etc., Berl. klin. Wchnschr. 822, 1899.

13. Munch-Petersen, H.: Die Hautreflexe und ihre Nervenbahnen, Deutsch. Ztschr. f. Nervenhe. 22:1902. Quoted by Yoshimura.¹⁷

14. Okada, E.: Ueber das Babinskische Zehenphänomen, Neurologia 1:13, 1902. Quoted by Yoshimura.¹⁷

15. Schüler, L.: Beobachtungen uber Zehenreflexe, Neurol. Centralbl. 19: 585, 1899.

16. Schneider, H.: Ueber das Zehenphänomen Babinski's, Berl. klin. Wchnschr., 1901.

17. Yoshimura, K.: Ueber das Babinskische Phänomen, Mittheilungen aus den Medizinischen Fakultät der Kaiserlichen Universität zu Tokyo 8:213, 1909.

18. Kornilow, A.: Ueber Cerebrale und Spinale Reflexe, Deutsch. Ztschr. f. Nervenhe. 23: 1903.

19. Tumpowski, A.: Ueber den diagnostischen Werth des Babinskischen Phänomens, Neurol. Centralbl. 20:663, 1901; abstr. from Medycyna (Polish).

20. Chodz'ko: Beitrag zur Bed. des Babinskischen phänomens, Abstr. from Gaz. lekarska, 1901, in Neurol. Centralbl. 20:663, 1901.

21. Passini, F.: Ueber den Normalen Grosszehenreflex bei Kindern, Wien. klin. Wchnschr. 952, 1900.

when the pyramidal tracts are not yet fully developed. When he came to test for this phenomenon in new-born infants, he found that his surmise was correct. Indeed, he believes that dorsiflexion of the toe is the normal plantar reflex in all children who have not yet learned to walk, but that when the child is able to walk the character of the reflex changes from dorsiflexion to plantar flexion. Cestan and Le Sourd found in all infants under 1 year old a dorsiflexion, but they failed to find the exact age at which the reflex changes from dorsiflexion to plantar flexion.

Collier found the age of transition in normal healthy children to be between 2 and 3 years. He says:

I have met with the typical adult response in children 2 years old who were particularly forward and "strong on their legs." In weakly and especially in rickety children, the infantile response may be as late as the age of 4 years.

During sleep, Collier finds the flexor response (i. e., plantar flexion) to be the rule even in infants, but in some children, even up to the age of 12 years, who showed plantar flexion when awake, there was dorsiflexion during sleep. Collier, like Babinski, associates this dorsiflexion of the toe in infants with imperfect myelination of the pyramidal system, and calls attention to the fact that in monkeys (in whom the pyramidal tracts are incompletely developed) the plantar reflex is dorsiflexor in type.

Schüler examined 100 children and found the following results:

No reflex response.....	in 40 per cent.
Dorsiflexion	in 30 per cent.
Plantar flexion	in 12 per cent.
Indefinite response.....	in 18 per cent

The 40 per cent. in which there was no response were all young infants. He concludes that in normally developed infants plantar flexion is the prevailing response during the fourth quarter of the first year but that the nature of the response varies with the general development of the infant. Thus an infant aged 14 months whose weight was only that of one aged 5 months, showed dorsiflexion, while a 5 months' old infant which was well developed showed plantar flexion.

Cohn, like Schüler, finds no response at all in about half the cases examined.

Gallewski ^{21a} set himself the task of discovering whether the Babinski reflex, whose clinical significance in adults cannot be doubted, is also to be correlated with the degree of development of the pyramidal tracts in infants. Utilizing the Weigert-Pal's method of staining

21a. Gallewski, M.: Histologische und klinische Untersuchungen über die Pyramidenbahn und das Babinskische Phänomen im Säuglings Alter. Dissertation Breslau 1902 (British Museum).

as modified by Kulschitzky, he finds that there is a definite parallelism between myelination and function in the pyramidal system as measured by the presence or absence of Babinski's sign. He examined nine infants between birth and 8 months of age and found that in all of them, except one (case 6) the reflex was dorsiflexor in type and they all showed greater or less poverty in myelin in the pyramidal regions (the degree of myelination varying with the age of the infant).

One child (Case 6) presented an extreme atrophy (only weighing 2,070 gm., i. e., about 4½ pounds), but the reflex was plantar flexor in character. The pyramidal tracts, both crossed and direct, were very poorly myelinated so that microscopically they resembled the picture shown in the case of an infant one month old.

Here, then, is a case which apparently militates against Babinski's theory. In order, however, to bring the case into line with that theory, Gallewski calls to his aid Kalischer's explanation of the Babinski phenomenon. Kalischer believes that those muscles which are less well innervated will respond reflexly in preference to an antagonistic group of muscles whose innervation is better. In infants in whom the foot is still, atavistically, a prehensile rather than a progressional organ, the interossei are a stronger group of muscles than the extensors of the toes, and, therefore, as a result of reflex irritation the extensor hallucis responds. When the foot definitely becomes an organ of locomotion, the relative strength of the antagonistic groups of muscles becomes reversed and dorsiflexion is replaced by plantar flexion. In Case 6, which was one of extreme atrophy, Gallewski makes the unwarranted assumption that the interossei were more atrophied than the extensors, and thus plantar flexion is obtained.

Walton and Paul²² find no characteristic reflex in infants. Morse,²³ in an investigation of 254 infants not suffering from any nervous disease found no plantar reflex at all in ninety (35 per cent.); reflex absent on one side and plantar flexion on the other in eighteen (7 per cent.); reflex absent on one side and dorsiflexion on the other in fifteen (6 per cent.); plantar flexion on both sides in sixty-four (25.5 per cent.); dorsiflexion on both sides in fifty-four (21.5 per cent.); plantar flexion on one side and dorsiflexion on the other in thirteen (5 per cent.).

He found further that during the first nine months bilateral dorsiflexion was more frequent than plantar flexion, while after that age the condition was reserved. His findings are shown in Table 1.

22. Walton and Paul: Contribution to the Study of the Plantar Reflex, etc., *J. Nerv. & Ment. Dis.*, **27**:305, 1900.

23. Morse, J. L.: A Study of the Plantar Reflex in Infancy, *Pediatrics* **11**:13, 1901.

Morse concludes that (1) there is no constant plantar reflex in the first year; (2) there is no constant plantar reflex in the second year, although it approximates that of the adult; (3) the normal reflex is not established at 2 years.

Engstler^{23a} examined a large number (eighty-nine) of healthy infants²⁴ in Graz and found (mostly in the sleeping state) that (1) in premature and mature infants at birth, there was a typical dorsiflexion of the big toe in all cases; (2) during the first year 93 per cent. had dorsiflexion and only 7 per cent. plantar flexion, (3) between the second and third years, plantar flexion is 95 per cent.; (4) at the end of the first year, 50 per cent. had dorsiflexion and 50 per cent. had plantar flexion; (5) Babinski's sign becomes an abnormal phenomenon after the second year.

TABLE 1.—MORSE'S FINDINGS AS TO REFLEXES IN NORMAL INFANTS *

	Percentages First Year (200 Cases)	Percentages Second Year (54 Cases)
Plantar flexion on one side and dorsiflexion on the other	5 (8.5)	5.5 (6.5)
Plantar flexion on one side and no reflex on other..	7 (11.8)	7.5 (8.7)
Dorsiflexion on one side and no reflex on other....	6 (10.2)	5.5 (6.5)
No reflex on either side.....	41	15.0
Plantar flexion on both sides.....	16.5 (28)	57.5 (67.4)
Dorsiflexion on both sides.....	24.5 (41.5)	9 (10.9)

* The percentages in parentheses are those calculated after deducting the eighty-two cases in the first year and the eight cases in the second year which gave no reflex on either side.

Griffith²⁵ accepts Engstler and Leri's²⁶ statement that "the plantar reflex in the new-born is characterized by dorsal flexion of the toes" and that "gradually this condition changes, but it is not till the third year that plantar flexion is the rule."

Barnes²⁷ agrees with Kalischer that the change from dorsiflexion to plantar flexion occurs at the beginning of walking even if the latter is delayed to the age of 4 or 5 years; but he finds that the response in infants is not so strong as in severe spastic states in adults—proving that even at birth the pyramidal system is by no means functionless, although myelination of fibers has not occurred.

Leri finds in 166 infants aged from 1 day to 3 years that (1) at birth dorsiflexion is the practically general rule (in this way agreeing with Muggia's findings but disagreeing with Guidiceandrea). (2)

23a. Engstler, G.: Ueber den Fusssohlenreflex, etc., Wien klin. Wchnschr. 18:567, 1905.

24. The total number of cases he examined was 1,000 but 109 gave no response.

25. Griffith, J. P. C.: Diseases of Infants and Children, 1919.

26. Leri, A.: Le reflexe des orteils chez les enfants, Rev. neurol. 689, 1903.

27. Barnes S.: The Diagnostic value of the plantar reflex, Rev. neurol. & psych. 352, 1904.

After 3 years plantar flexion is the rule, although dorsiflexion may occur without any pathologic significance. (3) Between 1 and 3 years dorsiflexion is not met with, as a rule, except (a) in affections of the central nervous system; but in these cases it has not the same significance as in adults because the pyramidal tracts soon after their formation are still more susceptible to every slight irritation especially of a toxic character; (b) in severe disturbances of nutrition which produce a retardation of development of the pyramidal tracts. (4) The change from dorsi flexion to plantar flexion occurs in normal infants at about 5 or 6 months. (5) Plantar flexion is of more diagnostic significance than dorsiflexion since in children in whom walking starts late it remains the only sign that the pyramidal tract is properly developed and that there is no fear in them of Little's disease.

Finizio²⁸ studied the reflex in 500 new-born infants during the first three days of life. He found no reflex in 5 per cent.; indecisive reflex in 10 per cent.; dorsiflexion in 15 per cent.; plantar flexion in 70 per cent. Finizio also studied the modified plantar reflexes (Schaffer's and Brissaud's reflexes) and found both of them present at birth.

As regards the effect of labor on the character of the reflex, Finizio finds that in difficult forceps cases there is dorsiflexion—possibly because in such cases some meningeal hemorrhage is produced. In true Little's disease, however, he finds plantar flexion. Sometimes in forceps cases he found a brisk knee-jerk with a Babinski phenomenon on one side, and plantar flexion on the other, possibly from inequality of the pressure of forceps on the fetal skull.

Furmann²⁹ who investigated 502 infants and children found the plantar reflex absent only in twenty-four cases. He further found that in infants under 9 months old dorsiflexion of the toe is almost the rule, while the transition from dorsiflexion to plantar flexion occurs between 9 months and 2 years. According to this observer, the occurrence of a Babinski phenomenon after the age of 2 years is indicative of an affection of the pyramidal tracts.

Laurent³⁰ found in 110 children between a few hours and 3 years old a constant Babinski phenomenon during the first six months, and one alternating with a normal plantar reflex between 6 months and 15 months. After that age an extensor (dorsiflexor) response is, according to him, very rare, except pathologically.

28. Finizio, G.: *Le Reflex de la plante du pied chez les Nouveaux*, XIII Cong. Internat. de Med., Compt. Rend. Sect. med. de l'enfance; Paris, 1900, p. 399.

29. Furmann: *Die Reflexe des Säuglings*, Dissertation St. Petersburg, 1903; abstr. by Gundobin in *Die Besonderheiten des Kindesalters*, Berlin, 1912.

30. Laurent, R.: *Evolution des reflexes chez l'enfant*, These de Toulouse, 1905; abstr. in *Brit. J. Child. Dis.* 460, 1906.

OBJECTS OF THE PRESENT INVESTIGATION

As there are wide divergences in the findings of the nature of the plantar reflex in infants and the age at which the reflex becomes definitely of the adult type, I have investigated about 500 children from birth (including premature births) up to the age of 8 years, with the following objects:

1. To test the truth of the generally accepted statements (a) that dorsiflexion is the prevailing phenomenon during infancy; (b) regarding the dependence of the nature of the plantar reflex on the state of the development of the pyramidal tracts as found postmortem.

2. The conformation of the postmortem findings with theoretical expectations.

3. To find the correlation (if any) between the response and various developmental and environmental states.

4. Localization of the reflexogenetic zone in infants.

Nature of the Material.—The material on which this research has been carried out consisted mainly of infants brought to the outpatient department of the Infants Hospital. Some observations, however (especially those at birth), have been made in private cases as well as in a few instances in cases at the Chelsea Infirmary. For the last I am indebted to my cousin, Dr. Victor Feldman, assistant medical officer at that institution, for having kindly allowed me to make the observation.

Method of Investigation.—In all cases, the observations were made when the feet were warm, i. e., after they (as well as the infant) had been well wrapped up in a blanket. The stimulus was applied by means of the thumb nail. In some cases, in order to warm the feet, it was necessary to sponge them with warm water. In a case in which I assisted at the birth of the child, I had the opportunity in a transverse presentation to test the reflex intra-uterinally by enclosing the ankle between ring and middle fingers, stimulating the sole of the foot with the thumb and feeling the direction of the toe with the index finger. In the case of older infants it was often found necessary to pacify them by means of the breast or the bottle before testing for the reflex in order to avoid the error between a true Babinski phenomenon and the movements of the toes and foot which often occur as a defensive mechanism against the irritation and which is not unlike the Babinski reflex. The plantar defense reaction consists in rapid dorsiflexion of the foot with simultaneous withdrawal of the foot from the source of irritation, with or without extension of the big toe. In a true Babinski phenomenon the great toe extends slowly. In some cases the reflex was tested during sleep. It often happened that there was, at first, no response of the toes at all to the plantar stimulus, but frequent repetition of the stimulus very rarely failed, although it did sometimes fail, to elicit some sort of a response.

I have no exact record of the number of cases at every age period which failed to give a response, but as the total number of cases examined was about 500 and of these 426 gave some sort of response, the total percentage of absent reflexes was about 15.

Results.—In the following tables I have classified my results in 426 cases from birth onward in which a response was obtainable. From these it is seen that:

1. During the first year, the proportion between flexor and extensor responses is approximately 4:1 and that in approximately 16 per cent. the reflex is variable, being either different in the two sides or different on each side at different times.

2. During the second year, the proportion between flexor and extensor responses is approximately 3:1 and in about 14 per cent. the reflex is variable.

3. During the third year, in 81 per cent. of cases the response was plantar flexor in type, and in 19 per cent. it was variable. There were no cases with a constant bilateral Babinski phenomenon.

4. During the fourth year the proportion between flexor and extensor responses was 14:1, and in 5 per cent. of cases it was variable.

5. After the fourth year, there was only one case (Case 617) in which there was an extensor response on one side, in all the remaining eleven cases the response was invariably plantar flexor in type on both sides. I have, however, notes of one case, a boy, aged 9 years and 4 months, in which the reflex was the typical Babinski phenomenon (Case 753). This boy was brought to me because he walked on tiptoe. There was no history of obstetric difficulties at birth. He began to walk and talk at the normal periods, but he walked on his toes from the beginning. There is a history of several miscarriages by his mother both before and after the birth of this child, and some time before this child was born the mother passed through a typical spurious pregnancy and labor.

On examining the child I found him to be a bright, intelligent boy. His weight was 6 stone (84 pounds) and his height 4 feet 6 inches. He preferred to walk on his toes, but was also able to walk on the soles of his feet normally. His knee jerks as well as the other reflexes were not increased, and there was no ankle clonus, but the plantar reflex was typically dorsiflexor in type. The flexors of the leg, however, were tense. It is possible, therefore, that this is a mild case of Little's disease, although there is no other evidence to substantiate the diagnosis.

I have summarized the findings of various observers, but it must be noted that the groups of cases are not strictly comparable as regards age.

TABLE 2.—DATA ON FLEXION BY VARIOUS OBSERVERS

	Engstler (891 cases)	Schüler (60 cases)	Morse (194 cases)	Finizio (500 new-born)	Feldman (426 cases)
Plantar flexion.....	26.7%	20%	39%	73%	67.0%
Dorsi flexion.....	73.3%	50%	33%	16%	16.4%
Indefinite.....	30%	28%	11%	16.6%

These figures have been calculated after deducting the numbers of cases, in each series, in which the reflex was absent.

Age at Which the Sign Disappears.—While it would be impossible to say definitely that dorsiflexion never occurs after the sixth year in a child whose pyramidal tracts are not diseased, I have been unable to elicit it in any one of a considerable number of cases in which I have looked for it after that age. Case 777 is the only one among a dozen or more cases of children of that age in which there was dorsiflexion of the toe on one side (right). On the other hand, Case 618 was a normal girl, 4 years old, who had marked dorsiflexion of the toe seven hours after a convulsive seizure.

Correlation Between Response and the State of Development of the Pyramidal Tracts as Found Postmortem.—In two cases in which I had records of the nature of the plantar response I had an opportunity of examining sections of the spinal cord postmortem, after keeping in Müller's fluid for six weeks, and staining sections by Weigert-Pal's method.

CASE 1 (128).—This was a case of congenital deformity. Both tibiae were curved. The fibulae were absent and no definite tarsal bones could be made out radiographically. The feet were practically suspended from the legs in the same straight line. The infant was extremely wasted, having weighed only 5 pounds 3 ounces at one month, and about the same weight at death at the age of 7 weeks. The plantar reflex was absent on the right side and plantar flexor in type on the left side throughout its life. It died at the age of 7 weeks. The cord showed the presence of some myelinated fibers in all the white columns and in each region (cervical, dorsal and lumbar), although myelination was incomplete in the crossed pyramidal tracts in the lower region. There was no noticeable difference in the state of myelination of the two sides of the cord, in spite of the difference in response. As, however, the response was altogether absent on the right side, the fault could not rest in the pyramidal tract but in the lower neuron. Moreover, the anterior horn cells being developed early in the fetus, the fault must have been in the peripheral nerves. The brain was of good size and showed no abnormality. There was only one kidney which was horseshoe shaped, although there were two suprarenals.

CASE 2 (614).—This was a male child whose weight at birth was 8 pounds. The plantar reflex was flexor (i. e., plantar flexion) on both sides at the age of 14 hours, and flexor on one side and extensor (i. e., dorsiflexion) on the other at 28 hours. It died suddenly at the age of 35 hours. Postmortem the thymus was found to be 11.6 gm. in weight (i. e., about normal). The spinal cord showed some myelination of all the white columns although the myelination was more incomplete in the crossed pyramidal tracts. There is no obvious difference in the degree of myelination between the two sides of the cord, in spite of the difference in the character of the response on the two sides.

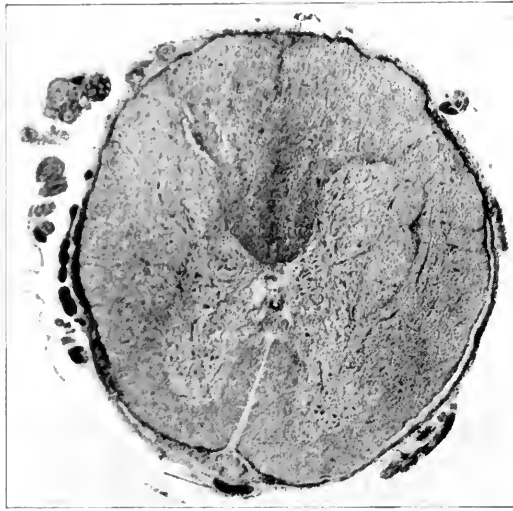


Fig. 1.—Photomicrograph of section of the dorsal cord region of the spinal cord from Case 614; $\times 14$.

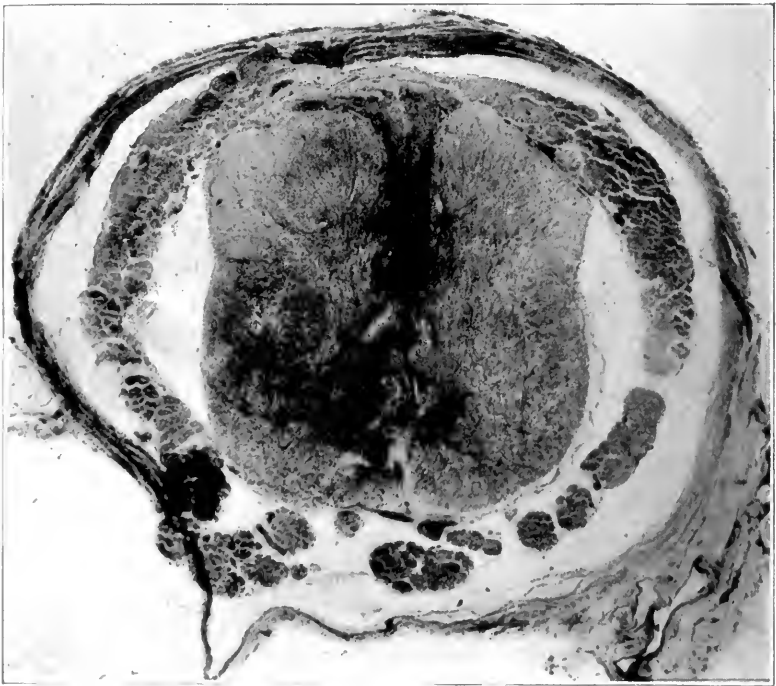


Fig. 2.—Photomicrograph of section of dorsal region of the spinal cord from Case 128; $\times 14$.

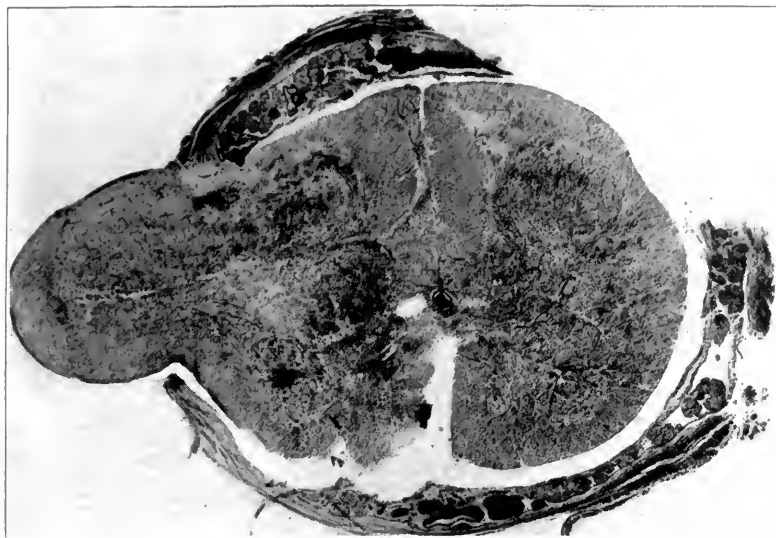


Fig. 3.—Photomicrograph of section of lumbar region of spinal cord from Case 614; $\times 14$. The cord was injured during its removal.

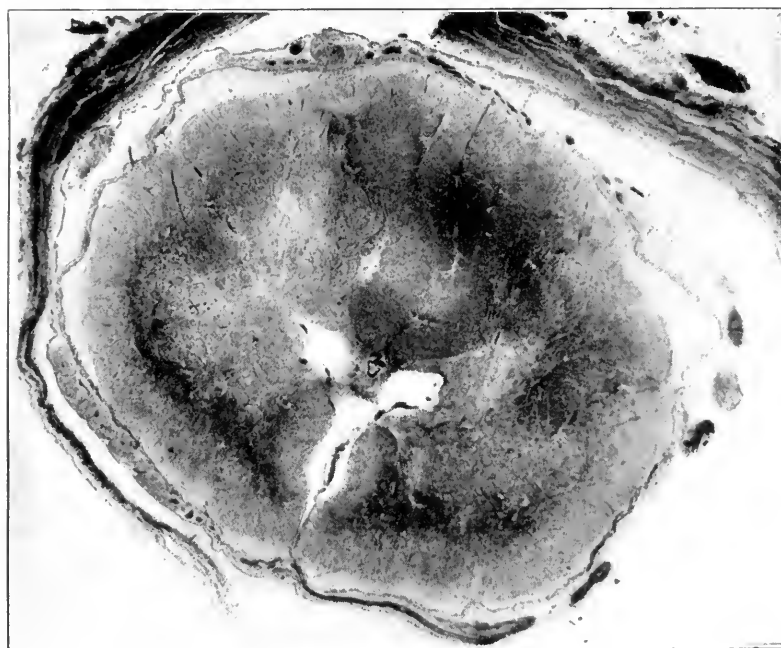


Fig. 4.—Photomicrograph of lumbar region of spinal cord from Case 128; $\times 14$.

On comparing the cords of Cases 128 and 614 there is obviously a greater poverty of myelin in Case 128 (the microphotographs do not show it so well as the slides examined by means of a projector), and yet in this case there was no dorsiflexion on either side although in Case 614 there was plantar flexion on the right side.

Hence, it appears that the degree of myelination of the pyramidal tracts in early infancy is not sufficient to explain the nature of the plantar response.

Moreover, the occurrence of a true Babinski phenomenon either on one side or on both sides after the age of 3 years in normally developed children, in whom according to all authorities the pyramidal tracts are fully developed, points to the same conclusion.

The inference that one is led to draw from these facts is that although the pyramidal tracts are not completely developed at birth, there is a sufficiency of myelination in them to give a normal flexor plantar response; but (as I shall show later) that in virtue of the greater susceptibility of children to reflex disturbances in the circulatory system, the pyramidal tracts may be compressed and relaxed alternately as the result of such circulatory disturbances.

What Factors, if Any, Influence the Nature of the Plantar Response in Infants?—Sex: The first factor that would occur to one is the influence of sex. I find that in very early infancy a normal flexor response is slightly more common in girls than in boys, but this may be accounted for by the paucity of numbers. If we take, however, all cases during the first six months, the first year, the first two years, etc., I find that there is an equality of plantar flexor responses in both sexes, although the extensor or dorsiflexor response is at all periods more common in girls than in boys to the extent of about 6 or 8 per cent (see Tables 4, 6, 8).

2. Prematurity (Table 5): The effect of prematurity is shown quite clearly in Table 5.³¹ (a) During the first month no less than six out of eight cases showed a Babinski phenomenon on each side, one only a bilateral plantar flexion, and the other case showed plantar flexion on one side and dorsiflexion on the other. (b) After the fifth week the effect of prematurity begins to pass off, although if the prematurity is very great, its effect is more lasting (Case 738, at the age of 7 months). Throughout the first year thirteen out of thirty-eight infants prematurely born had a positive Babinski phenomenon (34 per cent.). (c) The E: F ratio which is 6: 1 during the first month becomes 1: 4 during the second month and 1: 6 during the third. It still keeps on falling during the second quarter but remains stationary after that.

31. See especially the E: F rates in Table 5, which is very instructive.

TABLE 3.—INCIDENCE OF THE VARIOUS RESPONSES AT DIFFERENT AGES
FROM BIRTH ONWARDS

Age	No. of Cases	F	E	V		No. of Cases	F	E	V
At birth.....	5	3	1	1	First week.....	12	7	3	2
First day.....	3	2	1	1					
Second day....	1	1					
Third day.....	1	1					
Fifth day.....	2	1	1	..					
1-2 weeks.....	2	1	1	..	Second week.....	10	5	4	1
2 weeks.....	8	4	3	1					
2-3 weeks.....	4	3	1	..	Second half of month..	22	14	5	3
3 weeks.....	6	3	1	2					
4 weeks.....	12	8	3	1	First month.....	44	26 (59%)	12 (27.3%)	6 (13.7%)
5 weeks.....	14	10	2	2	Second month.....	79	63 (80%)	7 (8.8%)	9 (10.2%)
6 weeks.....	18	15	2	1					
7 weeks.....	13	9	..	4	Total first 2 mos.	123	89 (72.4%)	19 (15.4%)	15 (12.2%)
8 weeks.....	34	29	3	2	Third month.....	72	39 (54.2%)	23 (32%)	10 (14.8%)
9 weeks.....	6	3	1	2					
10 weeks.....	17	10	6	1	Total first quarter...	195	128 (65.6%)	42 (21.5%)	25 (12.9%)
11 weeks.....	7	2	4	1	Second quarter.....	80	55 (68.8%)	9 (11.2%)	16 (20%)
12 weeks.....	42	24	12	6					
14 weeks.....	8	6	..	2	Total first half year..	275	183 (66.5%)	51 (18.5%)	41 (15%)
4 months.....	30	17	8	5	Third quarter.....	38	25 (66%)	5 (13%)	8 (21%)
5 months.....	19	13	1	5					
6 months.....	23	19	..	4	Total first 9 mos.	313	208 (66.4%)	56 (17.9%)	49 (15.7%)
7 months....	16	12	1	3	Last quarter.....	23	16 (70%)	2 (8.7%)	5 (21.3%)
8 months....	13	7	1	5					
9 months....	9	6	3	..	Total first year.....	336	224 (66.7%)	58 (17.3%)	54 (16%)
10 months....	8	8	First quarter 2d year..	22	12	6	4
11 months....	10	6	1	3					
12 months....	5	2	1	2	Second quarter 2d yr..	12	8	2	2
1 yr. 1 mo. ...	12	4	5	3					
1 yr. 2 mos. ...	6	4	1	1	Total 1st half 2d year	34	20 (59%)	8 (23.5%)	6 (17.5%)
1 yr. 3 mos. ...	4	4	Third quarter 2d yr. ...	10	8	1	1
1 yr. 4 mos. ...	3	3					
1 yr. 5 mos. ...	3	..	1	2	Fourth quarter 2d yr. ...	12	9	2	1
1 yr. 6 mos. ...	6	5	1	..					
1 yr. 7 mos. ...	3	2	..	1	Total 2d half 2d yr. ...	22	17 (72.7%)	3 (18.2%)	2 (9%)
1 yr. 8 mos. ...	3	3	Total whole of 2d yr. ...	56	37 (66%)	11 (20%)	8 (14%)
1 yr. 9 mos. ...	4	3	1	..					
1 yr. 10 mos. ...	3	1	2	..	Total whole of first 2 years.....	392	261 (66%)	69 (17%)	62 (16%)
1 yr. 11 mos. ...	8	2	..	1	Third year.....	16	13 (81%)	..	2 (19%)
2 years.....	6	6					
2-2½ years...	7	6	..	1	Fourth year.....	5	3	1	1
2½-3 years...	9	8	..	1					
3-4 years.....	5	3	1	1	Total first 4 yrs.	413	277 (67%)	70 (17%)	65 (16%)
4-9 years.....	13	11	0	2	13	11	..	2
					Total first 9 yrs.	426	288 (67.6%)	70 (16.4%)	67 (16%)

TABLE 4.—INFLUENCE OF SEX ON THE NATURE OF THE PLANTAR REFLEX

Age	Males				Females			
	No. of Cases	F	E	V	No. of Cases	F	E	V
0.....	2	1	..	1	3	2	1	..
First day.....	2	1	1	..	1	1
Second day.....	1	1	0
Third day.....	0	1
5 days.....	2	1	1	..	0
First week.....	7	3	2	2	5	4	1	..
1-2 weeks.....	0	2	1	1	..
2 weeks.....	2	..	2	..	6	4	1	1
Second week.....	2	..	2	..	8	5	2	1
2-3 weeks.....	4	3	1	..	0
3 weeks.....	6	3	1	2	0
Third week.....	10	6	2	2	0
4 weeks.....	9	7	1	1	2	1	1	..
First month.....	28	16 (57%)	7 (25%)	5 (18%)	15	10 (67%)	4 (27%)	1 (6%)
5 weeks.....	8	6	..	2	6	4	2	..
6 weeks.....	6	5	..	1	10	8	2	..
7 weeks.....	7	4	..	3	6	5	..	1
8 weeks.....	16	13	1	2	18	16
Second month.....	37	28 (75.7%)	1 (2.6%)	8 (21.7%)	40	33 (82.5%)	6 (15%)	1 (2.5%)
9 weeks.....	2	1	..	1	3	2	1	..
10 weeks.....	9	5	3	1	8	5	3	..
11 weeks.....	6	2	3	1	1	..	1	..
12 weeks.....	27	16	7	4	15	8	5	2
Third month.....	44	24 (54.5%)	13 (30%)	7 (15.5%)	27	15 (55.5%)	10 (37%)	2 (7.5%)
Total first 3 months....	109	68 (62.5%)	21 (19.2%)	20 (18.2%)	82	58 (70.7%)	20 (24.4%)	4 (4.9%)
14 weeks.....	6	5	..	1	2	1	..	1
4 months.....	17	11	3	3	13	6	5	2
5 months.....	8	5	..	3	10	7	2	1
6 months.....	15	13	..	2	7	5
Second quarter.....	46	34 (74%)	3 (6.5%)	9 (19.5%)	32	19 (60%)	7 (22%)	6 (18%)
Total first half year....	155	102 (65.8%)	24 (15.5%)	29 (18.7%)	114	77 (67.6%)	27 (23.7%)	10 (8.7%)
7 months.....	11	8	1	2	5	4	..	1
8 months.....	6	3	..	3	7	4	1	2
9 months.....	8	5	3	..	1
Third quarter.....	25	16 (64%)	4 (16%)	5 (20%)	18	9 (70%)	1 (7.7%)	3 (22.3%)
10 months.....	2	2	6	6
11 months.....	6	3	1	2	3	2	..	1
12 months.....	1	1	1	1
Fourth quarter.....	9	6 (66.6%)	1 (1.1%)	2 (2.2%)	10	9 (90%)	..	1 (10%)
Total second half of first year.....	34	22 (64.7%)	5 (14.7%)	7 (20.6%)	23	18 (78.3%)	1 (4.4%)	4 (17.3%)
Total whole of first year.....	189	124 (65.6%)	29 (15.4%)	36 (19%)	137	95 (70%)	28 (20%)	14 (10%)
Second year.....	26	20 (77%)	2 (7.7%)	4 (15.3%)	28	16 (57%)	9 (32.2%)	3 (10.8%)
Total first 2 years.....	215	144 (67%)	31 (14.4%)	40 (18.6%)	165	111 (67.3%)	37 (22.4%)	17 (11.3%)
Third and fourth years	11	9	..	2	9	5	1	3
Total first 4 years.....	226	153 (67.6%)	31 (13.7%)	42 (18.7%)	174	116 (66.6%)	38 (21.8%)	20 (11.6%)
Cases over 4 years.....	8	5	1	2	6	6
Total.....	234	158 (67.5%)	32 (13.6%)	44 (19%)	180	122 (67.8%)	38 (21.5%)	20 (11.1%)

3. Degree of Development of the Infant as Determined by Length and Weight (Tables 6 and 7): It has been stated by a number of observers, e. g. Leri, Schüler and others that the Babinski phenomenon is more common in poorly developed than in well developed infants. I have therefore analyzed my cases according to their weights as well as according to their lengths.

TABLE 5.—EFFECT OF PREMATURITY

Age	No. of Cases	F	E	V	E:F Ratio
First week.....	3	1	2	..	6:1
2 weeks.....	2	..	1	1	
3 weeks.....	1	..	1	..	
4 weeks.....	2	..	2	..	
First month.....	8	1 (12.5%)	6 (75%)	1 (12.5%)	6:1
5 weeks.....	1	..	1	1	1:4
6 weeks.....	1	1	
7 weeks.....	3	3	
8 weeks.....	
Second month.....	5	4 (80%)	1 (20%)	..	1:4
9 weeks.....	1	1	1:6
10 weeks.....	2	2	
11 weeks.....	2	..	1	1	
12 weeks.....	4	4	
Third month.....	9	6 (66.6%)	1 (11.1%)	2 (22.2%)	1:6
First 3 months.....	22	11 (50%)	8 (36.3%)	3 (13.7%)	7:10
4 months.....	3	1	2	..	4:10
5 months.....	1	1	
6 months.....	3	3	
Second quarter.....	7	5 (71%)	2 (29%)	..	
Total first 6 months.....	29	16 (55.3%)	10 (34.5%)	3 (10%)	
7 months.....	3	1	1	1	6:10
8 months.....	1	1	
9 months.....	3	1	2	..	
10 months.....	2	2	
11 and 12 months.....	
Total second 6 months...	9	5 (55.5%)	3 (33.3%)	1 (11.1%)	
Total first year.....	38	21 (55.2%)	13 (34.2%)	4 (10.5%)	6:10

Weight: It is difficult to say exactly what weight at any particular age can be considered abnormally low, but I think it will be agreed that infants under 5 pounds during the first week, under 6 pounds at a month old, under $7\frac{1}{4}$ pounds at 2 months, under $8\frac{1}{2}$ pounds at 3 months, under 11 pounds at 6 months and under 16 pounds at 1 year are considerably under weight. In the tables I have classified the infants according to these arbitrary standards, and I have also indicated what I considered below normal at intermediate ages. The detailed results are shown in the tables (Table 6), but dividing the cases into three monthly periods we obtain the following figures:

(a) During the first three months, there was a total of 133 cases of more or less normal development out of which ninety (67.7 per cent.) showed a normal (i. e., plantar flexion) reflex; twenty-five (18.8 per

TABLE 6.—INFLUENCE OF STATE OF DEVELOPMENT OF INFANT AS JUDGED FROM ITS WEIGHT

Age	Well Developed				Under Normal Development				Pounds
	No. of Cases	F	E	V	No. of Cases	F	E	V	
0.....	4	3	0	1	1	0	1	..	
First day.....	3	2	1	
Second day.....	1	1	
3 days.....	1	1	1	..	
5 days.....	2	1	1	0	
First week.....	9	6	1	2	3	1	2	0	Under 5
Second week.....	1	1	1	..	1	..	
2 weeks.....	5	4	1	..	3	1	2	1	Under 5½
3 weeks.....	4	2	0	2	2	1	1	..	Under 5¼
4 weeks.....	9	7	2	0	3	1	1	1	Under 6
Total first month...	28	20	4	4	12	4	7	2	
5 weeks.....	10	7	1	2	4	3	1	..	Under 6½
6 weeks.....	13	10	2	1	2	2	Under 6¾
7 weeks.....	10	6	..	4	3	2	..	1	Under 7
8 weeks.....	28	23	3	2	6	6	Under 7¼
Total first 2 mos. ...	89	66	10	13	27	17	9	3	
9 weeks.....	3	1	1	1	3	2	..	1	Under 7½
10 weeks.....	10	4	5	1	7	6	1	..	Under 8
11 weeks.....	2	..	2	..	5	2	2	1	Under 8¼
12 weeks.....	25	16	6	3	15	8	4	3	Under 8½
Total first 3 mos. ...	129	87 (67.4%)	24 (18.5%)	18 (14.1%)	57	35 (60%)	15 (26%)	8 (14%)	
3½ months.....	5	4	..	1	3	2	..	1	Under 8¾
4 months.....	22	14	5	3	7	3	2	2	Under 9
5 months.....	13	11	1	1	6	2	1	3	Under 10
6 months.....	13	10	..	3	8	7	..	1	Under 11
Total second 3 mos. ...	53	39 (73.6%)	6 (11.3%)	8 (15.1%)	24	14 (58.3%)	3 (12.5%)	7 (29.2%)	
Total first 6 mos. ...	182	126 (69.2%)	30 (16.1%)	26 (14.7%)	81	49 (70%)	18 (22%)	15 (18%)	
7 months.....	10	9	1	..	6	3	..	3	Under 12
8 months.....	7	5	..	2	5	2	..	3	Under 13
9 months.....	2	1	1	..	7	5	2	..	Under 14
10 months.....	3	3	4	4	Under 14½
11 months.....	8	4	1	3	2	2	Under 15
12 months.....	4	1	1	2	1	1	Under 16
Total second 6 mos. ...	34	23 (67.6%)	4 (11.7%)	7 (20.6%)	25	17 (68%)	2 (8%)	6 (24%)	
Total first year.....	216	149 (70%)	34 (16%)	33 (14%)	106	64 (61.3%)	20 (18.8%)	21 (19.8%)	
First half 2d year.....	12	6	4	2	21	4	3	..	Under 17½ at 13 mo. under 20 at 18 mo.
Second half of 2d year	7	5	1	1	9	9	Under 21 at 19 mo. under 23 at 2 yr.
Total second year...	19	11 (58%)	5 (26%)	3 (16%)	30	23 (76.6%)	4 (30.3%)	3 (10%)	

cent.) showed a Babinski phenomenon and the remaining eighteen (13.5 per cent.) had a reflex of a variable character. Of the fifty-seven cases definitely under standard weight, thirty-four (60 per cent)

showed a plantar reflex of the normal adult type, fifteen (26 per cent.) presented a Babinski sign, and eight (14 per cent.) had a variable reflex.

(b) During the first six months there is again a greater percentage of Babinski phenomena in poorly nourished than in well nourished infants (22.2 per cent. against 16.6 per cent.).

(c) During the first year there is still a preponderance of Babinski signs in favor of badly nourished infants, but this preponderance is not so great as during the earlier periods (19 per cent. as against 16 per cent.).

TABLE 7.—INFLUENCE OF STATE OF DEVELOPMENT AS JUDGED FROM LENGTH

Age	Well Developed				Under Normal Development				Inches
	No. of Cases	F	E	V	No. of Cases	F	E	V	
0-4 weeks.....	13	10	2	1	7	4	2	1	Under 19
1-2 months.....	58	44	6	8	16	14	1	1	Under 20
2-3 months.....	52	29	16	7	17	9	5	3	Under 20½
Total first 3 mo.	123	83 (67.4%)	24 (19.5%)	16 (13%)	40	27 (67.5%)	8 (20%)	5 (12.5%)	
3-4 months.....	29	19	6	4	6	2	1	3	Under 20½
5 months.....	16	12	..	4	2	1	1	..	Under 21
6 months.....	17	13	..	4	4	4	Under 22
Second quarter.....	62	44 (71%)	6 (9.6%)	12 (19.2%)	12	7 (58.3%)	2 (16.6%)	3 (25%)	
Total first half year	185	127 (68%)	30 (16%)	28 (15%)	52	34 (65%)	10 (19%)	8 (15.5%)	
7 months.....	10	9	1	..	5	2	..	3	Under 23
8 months.....	11	6	5	..	1	1	Under 23½
9 months.....	6	4	2	..	3	2	1	..	Under 24
Third quarter.....	27	19	8	..	9	5	1	3	
10 months.....	5	5	1	1	Under 24
11 months.....	9	5	1	3	Under 24½
12 months.....	3	2	1	Under 25
Last quarter.....	17	12	1	4	1	1	
Total second 6 mos.	44	31 (70%)	9 (20%)	4 (10%)	10	6 (60%)	1 (10%)	3 (30%)	
Total first year.....	229	158 (69%)	39 (17%)	32 (14%)	62	40 (64.5%)	11 (17.7%)	11 (17.7%)	

From these facts it would seem, therefore, that malnutrition is a factor which operates against the production of a normal plantar flexor response. On analyzing the cases further, however, it is seen that such a conclusion is erroneous. We find that:

(d) During the period from 4 to 6 months there is a practically equal percentage of Babinski signs in the two groups of cases (12.5 per cent. in underdeveloped and 11.3 per cent. in well developed infants), while during the second semester there is actually a greater percentage of Babinski phenomena in normally developed infants than in infants below the standard (11.7 and 8 per cent, respectively).

(e) The same is the case during the period from 1 to 2 years (the percentage of Babinski phenomena in the normal and below normal groups of cases being 26 and 13.5 per cent., respectively).

It is, therefore, clear that malnutrition per se has no influence on the nature of the plantar response, but that inasmuch as during the early months prematurity and malnutrition go hand in hand, it is probably the prematurity and not the malnutrition that is responsible for the greater presence of Babinski phenomena in the undernourished infants. Indeed, if we subtract from the fifty-seven infants under normal weight during the first three months the seventeen which owed their defective weight to prematurity, and out of which seven had a plantar flexor response, seven a true Babinski sign and three a variable response, we obtain the following figures:

Total number of under weight cases, forty; normal adult type of response, twenty-seven (67.5 per cent.); Babinski sign in eight (20 per cent.); variable reflex in five (12.5 per cent.), which are almost identically the same percentages as those prevailing amongst the normally developed infants.

Length: It is generally recognized that the length of an infant is a far better criterion of growth than is weight.³² I have, therefore, arranged my cases at each age period in two groups, viz., one in which the infants are approximately of the average length at that age and another in which the infants are considerably shorter than the average (Table 7). I have indicated in the tables the lengths which I consider to be definitely below the normal. We there see that

(a) During the first month, 77 per cent. of the normal cases (i. e., ten out of thirteen) had a normal plantar reflex, 15 per cent. (i. e., two out of thirteen) had a Babinski and 7½ per cent. gave a variable response, while of the seven cases under normal length at the same period 57 per cent. had a normal plantar reflex, 28.5 per cent. gave a Babinski phenomenon and 14.25 per cent. gave a variable response.

(b) During the first three months, out of 123 normal cases and forty cases below the normal length, the percentages of cases of normal, Babinski and variable reflexes were respectively identical in the two groups, viz., 67.5, 20 and 13 per cent.

(c) During the second quarter, there was a great percentage preponderance of Babinski phenomena in the case of infants below the standard length, but this may be accounted for by the paucity of the number of cases in the abnormal group.

(d) For the period from birth (0) to 6 months, the preponderance in the abnormal group was very small (19 as against 16 per cent.).

(e) During the third quarter there was a percentage preponderance of Babinski phenomena in favor of the normal group of cases but this again may be accounted for by the very small number of cases in the abnormal group.

32. Feldman, W. M.: *The Principles of Antenatal and Postnatal Child Physiology Pure and Applied*, London, 1920.

(f) For the period from birth (0) to 12 months, the respective percentages in the two groups were practically identical.

It is, therefore, reasonable to infer that just as in the case of weight, length in itself has no influence on the nature of the plantar reflex, and that the preponderance of Babinski phenomena during the first month was due to the prematurity which was the cause of deficient length.

Cephalic Index (i. e. $\frac{\text{Width of head}}{\text{Length of head}} \times 100$) (Tables 8 and 9).

A head which has an index of less than 79 is dolichocephalic or long-headed. An index of between 79 and 81 makes the head mesocephalic and one of over 81 makes it brachycephalic. In spite of the plasticity of the infant's head, it has been asserted by Boas³³ and Ripley³⁴ (and my own observations tend to confirm it) that after the neonatal period, when the effects of the obstetric molding on the infant's head has passed off, although the cephalic index slightly decreases with increasing age, yet the type of the head remains the same, i. e., a brachycephalic head will always remain brachycephalic, and so forth. Now, contrary to the opinion held by most anthropologists that the cephalic index is a racial character determined by heredity, Boas believes that the shape of the head is a character which is affected by environment—including intellectual activity, brachycephaly being the accompaniment of marked activity of the brain. Therefore, I thought it would be of some academic interest to investigate the influence of the cephalic index on the plantar reflex because if Boas' contention is true, and if further it is true, as it almost certainly is, that the cephalic index is unaffected by growth, then one ought to find that in cases of brachycephaly the plantar reflex should be more commonly of the normal adult type, while the Babinski phenomenon should be more frequently associated with a dolichocephalic head. In the statistics presented (Tables 8 and 9), I have, in order to avoid error, excluded all cases of infants under 6 weeks old in whom the shape of the head might still be undergoing change.

The following are the results:

1. During the first quarter, the incidences of the different responses for the three different shapes of head are almost respectively identical.

2. During the first half year the percentages of normal responses for the three different varieties of head are practically identical, and while the incidence of the Babinski phenomenon is practically the same for dolichocephalic and mesocephalic heads, that in the case of brachycephalic heads is perceptibly less than in the other two (viz., 10.5 per cent. as compared with about 17 per cent.).

33. Boas, F.: The Form of the Head as Influenced by Growth. *Am. Science*, n.s. 50; Changes in Bodily Forms of Descendants of Immigrants, Washington, 1910.

34. Ripley, W. Z.: *American Science*, n. s. 111:888, 889.

TABLE 8.—INFLUENCE OF SHAPE OF HEAD ON THE NATURE OF THE PLANTAR REFLEX

Age	Dolichocephaly				Mescephaly				Brachycephaly			
	No. of Cases	F	E	V	No. of Cases	F	E	V	No. of Cases	F	E	V
7 weeks.....	5	3	..	2	2	2	0	..	2	2
8 weeks.....	12	12	11	10	1	..	4	2	..	2
Second month.....	17	15	..	2	13	12	1	..	6	4	..	2
9 weeks.....	5	3	1	1	1	1
10 weeks.....	8	4	4	..	3	1	2	..	3	2	1	..
11 weeks.....	4	2	2
12 weeks.....	22	15	4	3	7	4	2	1	7	3	2	2
Third month.....	39	24	11	4	11	5	4	2	10	5	3	2
Total first quarter.....	56	39 (70%)	11 (20%)	6 (10%)	24	17 (71%)	5 (21%)	2 (8%)	16	9 (56%)	3 (19%)	4 (25%)
14 weeks.....	4	4	1	1
4 months.....	8	4	2	2	9	5	2	2	6	4	1	1
Fourth month.....	12	8	2	2	9	5	2	2	7	5	1	2
5 months.....	8	6	1	1	3	1	..	2	6	4	..	2
6 months.....	5	4	..	1	5	4	..	1	9	7	..	2
Second quarter.....	25	18 (72%)	3 (12%)	4 (16%)	17	10 (58.8%)	2 (11.7%)	5 (29.5%)	22	16 (72.7%)	1 (4.6%)	5 (22.7%)
Total first 6 months.....	81	57 (70%)	14 (17.3%)	10 (12.6%)	41	27 (66%)	7 (17%)	7 (17%)	38	25 (66%)	4 (10.5%)	9 (23.5%)
Third quarter.....	11	10	..	1	4	3	..	1	18	8	5	5
Fourth quarter.....	2	2	5	3	1	1	9	6	..	3
Total second 6 months.....	13	12	..	1	9	6	1	2	27	14	5	8
Total first year.....	94	69 (73.4%)	14 (14.8%)	11 (11.7%)	50	33 (66%)	8 (16%)	9 (18%)	65	39 (60%)	9 (13.8%)	17 (27%)
First half second year.....	6	5	1	..	8	6	1	1	14	9	1	4
Second half second year.....	5	5	4	3	1	..	9	7	..	2
Total second year.....	11	10	1	..	12	9	2	1	23	16	1	6
Total first 2 years.....	105	79	15	11	62	42	7	10	88	55	10	23
2-3 years.....	4	4	5	3	..	2
Total first 3 years.....	109	83 (76%)	15 (14%)	11 (10%)	67	45 (67.5%)	10 (18%)	12	88	55 (62.5%)	10 (11.3%)	23 (26.2%)

3. During the whole of the first year the percentages of normal and Babinski phenomena are again practically the same for the three different varieties of heads, although a Babinski phenomenon is somewhat less common among the brachycephalic group.

4. During the second year, the numbers are too few to make any comparison.

5. For the whole period of the first two years, we have the following figures:

Dolichocephaly: 105 cases. Out of these

79, or 75.2 per cent. had a normal reflex.

15, or 14.3 per cent. had a Babinski phenomenon.

11, or 10.5 per cent. had a variable reflex.

TABLE 9.—DOLICHO AND MESOCEPHALY; BRACHYCEPHALY

Age	Dolicho and Mesocephaly				Brachycephaly			
	No. of Cases	F	E	V	No. of Cases	F	E	V
First quarter.....	80	56	16	8	16	9	3	4
Second quarter.....	42	28	5	9	22	16	1	5
First 6 months.....	122	84 (69%)	21 (17%)	17 (14%)	38	25 (70%)	4 (10.5%)	9 (23.7%)
Third quarter.....	15	13	..	2	18	8	4	5
Fourth quarter.....	7	5	1	1	9	6	..	3
Second 6 months.....	22	18	1	3	27	14	5	8
Total first year.....	144	102 (70.8%)	22 (15.2%)	20 (14%)	65	39 (60%)	9 (30.8%)	17 (14%)
Second year.....	23	19	3	1	23	16	1	6
Total first 2 years.....	167	121 (71.2%)	25 (15%)	21 (12.5%)	88	55 (62.5%)	10 (11.3%)	23 (26.2%)
Third year.....	9	7	..	2
Total first 3 years.....	176	128 (72.7%)	25 (14.2%)	23 (13%)	88	55 (62.5%)	10 (11.3%)	23 (26.2%)

Mesocephaly: 62 cases. Out of these

42, or 67.7 per cent. had a normal reflex.

10, or 16.1 per cent. had a Babinski phenomenon.

10, or 16.1 per cent. had a variable reflex.

Brachycephaly: 88 cases. Out of these

55, or 62.5 per cent. had a normal reflex.

10, or 11.3 per cent. had a Babinski phenomenon.

23, or 26.2 per cent. had a variable reflex.

In other words, the incidence of a Babinski phenomenon is slightly less among the brachycephalic group than among the other two groups, suggesting that cerebral inhibition may be greater in that group of cases. The fact that no difference is shown during the first three months may possibly be accounted for on the supposition that the head has as yet not completely recovered from the effects of obstetric molding.

6. For all cases throughout the first three years the percentages are practically the same as for the first two years.³⁵

Influence of the Nature of the Infant's Food on the Nature of the Plantar Reflex.—(Table 10) It has been alleged that the reason why human milk contains more lecithin and lactose than that of the cow is because more lecithin and lipin derivatives of lactose are required by the quickly growing infant's brain and nervous tissues with their myelin sheaths than is required by the more slowly growing nervous

TABLE 10.—INFLUENCE OF NATURE OF FOOD UPON THE NATURE OF THE PLANTAR REFLEX

Age	Breast				Bottle			
	No. of Cases	F	E	V	No. of Cases	F	E	V
First month.....	12	7 (58.3%)	3 (25%)	2 (16.7%)	9	4 (44.4%)	4 (44.4%)	1 (11.2%)
Second month.....	16	6	6	4	7	5	..	2
Third month.....	13	3	8	2	11	4	5	2
First quarter.....	41	16 (39%)	17 (41%)	8 (20%)	27	13 (48.1%)	9 (33.3%)	5 (19.9%)
Fourth month.....	8	5	2	1	6	4	2	..
Fifth month.....	1	1	2	..	1	1
Sixth month.....	2	1	..	1	3	1	..	2
Second quarter.....	11	6 (54.5%)	2 (18.2%)	3 (27.3%)	11	5 (45.5%)	3 (37.3%)	3 (27.2%)
Total first 6 months...	52	32 (42.3%)	19 (36.5%)	11 (21.2%)	38	18 (46.3%)	12 (31.6%)	8 (21%)
Seventh month.....	5	4	..	1	2	2
Eighth month.....	3	2	..	1	1	1
Ninth month.....	2	..	2
Third quarter.....	10	6	2	2	3	3
Fourth quarter.....	3	2	..	1	9	6	1	2
Total second half year	13	8 (61.5%)	2 (15.4%)	3 (23.1%)	12	7 (58.3%)	1 (8.4%)	4 (33.2%)
Total first year.....	65	30 (46.1%)	21 (32.3%)	14 (21.6%)	50	25 (50%)	13 (26%)	12 (24%)
Second year.....	9	2	3	4	3	1	2	..
Total first 2 years.....	74	32 (43.2%)	24 (32.4%)	18 (24.4%)	53	26 (50%)	15 (28.3%)	12 (22.7%)

system of the calf.³² If that is true, and if it is also true, as it practically certainly is, that to a certain extent the nature of the plantar reflex depends on the degree of myelination of the pyramidal tracts, then we would expect that in infants artificially fed there should be a larger percentage of dorsiflexor responses than in those fed on the breast. This is not found to be the case.

35. In view of the fact that owing to the development of the frontal sinuses and the occipital protuberance in later life the cephalic index slightly decreases with age, it is, perhaps, safer to classify both the dolichocephalic and mesocephalic types in our series together as dolichocephalic. This I did in Table 9. The results again show a smaller percentage of Babinski phenomena in the brachycephalic group.

During every age period (except during the first month) breast fed infants show a slightly larger percentage of Babinski phenomena than bottle fed infants, showing that breast feeding per se does certainly not tend to diminish the incidence of the Babinski phenomenon *after* the first month. It is not safe to generalize from the few cases during the first month, but as the percentages of Babinski phenomena during that period are 25 and 44 per cent., respectively, in breast fed and bottle fed babies, it would seem that breast feeding during the first few weeks has a salutary effect on the development of the nervous system.

If, further, we transfer from the thirty-eight bottle fed infants during the first half year (of which eighteen gave a flexor, twelve an extensor and eight a variable response), the fourteen infants (from the second month onward) which were breast fed for a variable period between two weeks and two months after birth (and of which seven gave a flexor, four an extensor and three a variable response), to the fifty-two that were entirely breast fed (up to the time of the examination) during the first half year, we obtain the figures shown in Table 11.

TABLE 11.—INFLUENCE OF NATURE OF FOOD ON PLANTAR REFLEX

	No. of Cases	F	E	V
Bottle fed first 6 months.....	38	18	12	8
Subtract partly breast fed.....	14	7	4	3
Entirely bottle fed.....	24	11 45.6%	8 33.3%	5 21%
Total entirely breast fed first 6 months....	52	22	19	11
Add partly breast fed.....	14	7	4	3
Total breast fed (entirely or partly)...	66	29 44%	23 34.8%	14 21.2%

In other words, we still arrive at the same result, that whatever influence breast feeding may possibly have on the development of the pyramidal tracts during the first month it has no effect whatever on the subsequent development of these tracts.

Influence of Body Temperature (Table 12).—A consideration of certain facts with regard to the circulation, respiration, and the superficial area of the skin in the infant leads one to expect that changes in the body temperature might have some influence on the nature of the plantar reflex in early life.

I have already shown that at birth the pyramidal tracts of the spinal cord are sufficiently well developed to conduct inhibitory impulses from the brain which would tend to produce a normal plantar reflex, and that the production of a Babinski phenomenon in early life is favored by insufficient cerebral control (? e. g. in dolichocephaly), as well as other factors, such as circulatory disturbances which might cause slight pressure on the incompletely developed tracts.

TABLE 12.—INFLUENCE OF BODY TEMPERATURE

Age	Subnormal				Normal				Pyrexia			
	No. of Cases	F	E	V	No. of Cases	F	E	V	No. of Cases	F	E	V
5 days.....	2	1	1	..	2	..	1	..	2
6-7 weeks.....	4	2	1	1	4	3	1	1	2	1	..	1
8-9 weeks.....	3	2	8	6	1	1	2	1	..	1
10 weeks.....	3	1	2	..	6	4	1	1	1	1	..	1
11 weeks.....	2	2	10	7	2	1	1	1	..	1
12 weeks.....	5	3	..	2	6	5	..	1	1	6	..	1
13 weeks.....	1	6	1	..	19	16	1	2	2	1	1	..
14 weeks.....	1	1	1	..	5	2	1	1	1	1	1	..
15 weeks.....	4	3	1	..	10	5	5	..	1	2	1	..
16 weeks.....	2	..	2	..	3	1	1	1	2	2	1	..
17 weeks.....	10	6	4	..	24	15	5	4	3	3
Total first 3 months.....	44	29 (66%)	12 (27%)	3 (7%)	97	65 (67%)	18 (18.5%)	14 (14.4%)	18	13 (72%)	2 (11%)	3 (17%)
Fourth month.....	9	5	1	3	19	12	5	2	8	5	1	2
Fifth month.....	4	2	1	1	8	5	..	3	5	5	..	2
Sixth month.....	3	3	13	11	..	2	5	3
Second quarter.....	16	10 (62.5%)	2 (12.5%)	4 (25%)	40	28 (70%)	5 (12.5%)	7 (17.5%)	18	13 (72.3%)	1 (5.5%)	4 (22.2%)
First half year.....	60	39 (65%)	14 (23.3%)	7 (11.7%)	137	93 (67.9%)	23 (16.8%)	21 (15.3%)	36	26 (72.2%)	3 (8.3%)	7 (19.5%)
Second half year.....	11	7 (63.3%)	2 (18.2%)	2 (18.2%)	27	19 (70%)	1 (4%)	7 (25.8%)	13	9 (70%)	2 (15%)	2 (15%)
Total first year.....	71	46 (64.8%)	16 (22.5%)	9 (12.7%)	164	112 (68.3%)	24 (14.6%)	28 (17.1%)	49	35 (71.4%)	5 (10.2%)	9 (18.4%)
Second year.....	1	1	33	23	5	5	16	10	5	1
Total first 2 years.....	72	47 (65.3%)	16 (22.2%)	9 (12.5%)	197	135 (68.5%)	29 (14.7%)	33 (16.7%)	65	45 (69%)	10 (15.5%)	10 (15.5%)

Now let us consider the following facts: (1) Czerny and Kleinschmidt³⁶ have recently shown radiographically that in severe disturbances of nutrition, which are generally accompanied by a subnormal temperature, and in which the abdominal muscles become relaxed, the heart becomes actually smaller in size on account of the interference with the movements of the diaphragm, which during inspiration helps to drive blood out of the abdomen into the thorax; (2) the relation between the surface and volume (or weight) of the body is greater in the infant than in the adult,³² e. g. at birth the area of the cutaneous surface of the body per kilogram body weight is three times, and at one year twice that in the adult, and hence in cases of subnormal temperatures in which there is anemia of the skin there is a much greater congestion of the internal organs in the infant than there is in the adult.

Consequently, we would expect subnormal temperatures in infancy to bring about great venous congestion of all the internal organs, including the spinal cord, which would tend to produce a Babinski phenomenon. The opposite would be the case in conditions accompanied by pyrexia.

I have, therefore, classified my cases into three groups, viz. (1) those with subnormal temperatures (under 97 F.); (2) those with normal temperatures (between 97 and 99 F.), and (3) those with pyrexia (above 99 F.). The results are very striking (Table 11). They show that: At all periods from birth (0) to 3 months, from birth (0) to 6 months, and from birth (0) to 12 months, the incidence of cases of Babinski phenomena occurs in decreasing percentages in the subnormal, normal and supernormal temperature groups.

Influence of Certain Toxic Agents (see Protocols of Cases).—(1) Syphilis: Of six cases of congenital syphilis, during the first three months, five gave a normal adult type of response and one gave dorsiflexion on one side and plantar flexion on the other. The syphilitic virus, therefore, had no deleterious influence on the pyramidal tracts. Indeed, one would not, a priori, expect it to have. For syphilis among adults, while it may cause degeneration of the posterior columns (as in tabes), hardly ever causes degeneration of the pyramidal tracts, except secondarily to cortical degeneration (as in dementia paralytica). (2) Toxemia from the bowels: This does not seem to have any influence on the nature of the response. (3) Pertussis: It is believed by some that the attacks in whooping cough are due to toxic irritation of the vagus, but out of four cases of pertussis during the first two years, three gave a plantar flexor response and only one a dorsiflexion

36. Czerny and Kleinschmidt: Weiterer Beitrag zur kenntniss der Zirkulationsstörungen bei akuten Ernährungsstörungen der Säuglinge. Jahrb. f. Kinder. **84**:441, 1916.

of the toe. The number of cases is too few to generalize but it does not seem as if the pertussis toxin has any influence on the pyramidal tracts.

Other Factors.—(1) Rickets: has been alleged to retard the development of the pyramidal tracts. I do not find it to be the case. (2) Convulsions: Esmenard³⁷ finds that both during an epileptic fit in adults and soon after there is a Babinski phenomenon. In the case of infants suffering from convulsions, in the interval between fits there was a normal plantar reflex in all the four cases that came under my observation during the first two years of life, but in one case of convulsions and pertussis, in a girl, aged 4 years, there was a very marked Babinski phenomenon nine hours after a fit. (3) Sleep: most cases in which the reflex was examined during sleep were of the Babinski character.

DIFFUSION OF THE REFLEXOGENOUS ZONE

Bertolotti,³⁸ in 1904, and Laurent, in 1905, found that the area of skin, stimulation of which will produce a plantar reflex in normal infants, is not confined to the sole of the foot but is very diffuse. Thus in 10 per cent. of cases Bertolotti could elicit a downward movement of the toes on pinching the skin as high up as the abdomen, and in from 30 to 50 per cent. he elicited movement on pinching the skin in various parts of the leg and thigh (compare Oppenheim's, Gordon's and other modifications of the Babinski sign in adults). Laurent found a similarly great extension of the reflexogenous zone, but the abstract of his thesis (which is the only record of his results that has been accessible to me) does not state whether the response he obtained was a plantar flexion or dorsiflexion of the toes. Laurent further found that the extension of the zone tends to disappear after the age of 9 months. Yoshimura¹⁷ confirms the extensive diffusion of the zone in infancy.

I have no statistics to offer on the matter, but I have examined a considerable number of cases and can fully confirm the findings of these observers with regard to the remarkable diffusion of the reflexogenous zone in early life. In quite a large proportion of cases—certainly more than the 10 per cent. found by Bertolotti—I have been able to obtain a plantar reflex on pinching the skin of the abdomen, even at the age of 1 year and 3 months.

In most cases the response was flexor in type (i. e., plantar flexion) but occasionally an extensor response was elicited, even when the

37. Esmenard, J.: Contribution a l'etude du phénomène des orteils dans l'épilepsie. These de Paris, 1902.

38. Bertolotti, M.: Etude sur la diffusion de la zone reflexogene chez les enfants, Rev. neurol. 12:1160, 1904.

ordinary response was flexor. It is remarkable, however, that the response was almost in every case much more pronounced than when the stimulus was applied to the sole. After about eighteen months, the reflexogenous zone gradually shrinks. In two cases (Cases 759 and 766), in children between 3 and 4 years of age, in which the zone was localized to the sole of the foot, stimulation of the inner border produced plantar flexion of the big toe, while stimulation of the outer border evoked a dorsiflexion of the toe. This peculiarity was bilateral and constant in each case.

Another interesting fact is that although the reflexogenous zone is extensively diffused in a vertical direction, it is in the large majority of cases lateralized, i.e., pinching of the skin on one side will not, as a rule, produce a plantar response on the other side.

SUMMARY

I have examined the plantar reflex of about 500 subjects from birth up to the age of 7 years, the large majority being under 4 years. I have not recorded the exact number of cases at the various age periods in which no response could be elicited, because absence of a plantar reflex is not peculiar to infancy. In a good many cases in adults I have failed to obtain any plantar response. Moreover, absence of the response is entirely due to an affection or deficient development of the reflex arc and gives no information regarding the upper motor neuron with which alone I was concerned in this investigation. As, however, I was able to obtain a response in 426 cases, I conclude that the total percentage of nonresponses is about 15. In this respect, therefore, my figures are more in agreement with those of Engstler who, in a series of 1,000 cases found the reflex to be absent in 109 (11 per cent.), and of Finizio who among 500 new-born infants failed to elicit it in 5 per cent., than with the 35 per cent. of absent reflexes given by Morse, and 40 per cent. given by Schüller.

As regards the nature of the response, my findings agree very closely with those of Finizio. For while all other observers find the prevailing response to be of the Babinski type, both Finizio and myself find the proportion between plantar flexion and dorsiflexion to be approximately 4:1 (Table 1). I cannot, however, confirm Finizio's statement with respect to the influence of forceps delivery on the nature of the response, for while Finizio finds that in difficult forceps cases there is dorsiflexion of the toe, of the two new-born forceps cases in my series, one of which (Case 602) was a particularly difficult one and gave rise to a good deal of trauma, both gave a normal response (i. e., plantar flexion). But my numbers are too few to draw any conclusions. I give my results as I have found them.

As regards the age at which the plantar reflex definitely becomes plantar flexor in type, I cannot agree with the conclusions of some observers that it depends on the age at which the child begins to walk, since not only do I find plantar flexion to be the prevailing response before the walking age, but I have obtained it in a few cases either unilaterally or bilaterally, long after the child had begun to walk. Moreover, in the same infant you might at different times elicit either plantar flexion or dorsiflexion.

As regards the correlation between the degree of development of the pyramidal tracts and the nature of the response, and the influence of the various developmental and environmental factors on it, see pp. 3 and 4, as well as under "conclusions."

CONCLUSIONS

1. The prevailing plantar response in early life is plantar flexion of the big toe, although when a dorsiflexion of the toe occurs it has not the same significance as a similar response in the adult.

2. The pyramidal tracts are sufficiently developed at birth (in cases of birth at full term) to give a normal adult type of plantar reflex even intra-uterinally, but owing to easily aroused circulatory disturbances in early life, the consequent changes in the circulation in the region of the cord are sufficient to compress the incompletely myelinated pyramidal tracts to evoke a Babinski phenomenon either unilaterally or bilaterally.

3. In premature infants the response is nearly always of the Babinski type, up to 5 or 6 weeks postnatal life, because of the almost total absence of myelination of the pyramidal tracts.

4. Malnutrition, as judged by defective weight and length, is not in itself sufficient to give a Babinski sign, but inasmuch as prematurity and defective weight and length go hand in hand up to about 5 or 6 weeks, the Babinski phenomenon seen in badly developed infants up to that age is due to the prematurity rather than to the malnutrition.

5. Bilateral plantar flexion is at all ages as common in girls as in boys, but bilateral dorsiflexion is at all age periods in infancy more common in girls than in boys.

6. Breast feeding during the first few weeks of life probably tends to diminish the incidence of a bilateral Babinski phenomenon; this may be so owing to the greater percentage of lecithin and lactose in human milk which helps the more rapid myelination of the pyramidal tracts. After the first month or so breast feeding has no advantage in this respect over bottle feeding.

7. Toxic influences, either from the bowel or from other causes, do not affect the conductivity of impulses along the fibers of the pyramidal tracts.

8. Bilateral dorsiflexion of the toes is commoner in cases with a subnormal temperature because, probably, in such cases there is a greater congestion of the spinal cord as the result of: (a) the pallor of the skin, whereby a relatively much larger quantity of blood goes to the internal organs (including the spinal cord) than in adults; (b) the interference with the action of the diaphragm and consequently of the pumping action of the heart in cases of severe disturbances of nutrition—which are frequently the accompaniments of subnormal temperatures.

9. Bilateral dorsiflexion is slightly more common in dolichocephalic than in brachycephalic infants, possibly because inhibitory control is less powerful in the former than in the latter.

10. Rickets does not favor the occurrence of a Babinski phenomenon.

11. The age at which the Babinski sign vanishes has no relation to the age at which the child begins to walk. In the majority of cases of very young infants who cannot even sit up the Babinski sign is absent, and in the cases of a large number of children who can walk and are "strong on their legs" (in some even during the third and fourth years) the Babinski sign is present.

12. As the peripheral nerves are imperfectly myelinated at birth³² a possible explanation of a Babinski phenomenon in certain infants is more imperfect development of the lower motor neuron supplying the flexors of the toes but better development of the neuron supplying the extensors. In such cases, of course, extension is the only possible movement.

13. The inconstant nature of the response in certain infants in whom at the same examination one may obtain on one stimulation a plantar flexion and on another stimulation of either the same or a different cutaneous area a dorsiflexion may be due to the easy fatigability, as well as easy recovery from fatigue of muscle in early life, so that after a certain response has been obtained the muscles producing that response can no longer contract as easily as the opposing groups of muscles and the response is, therefore, produced by the less fatigued group of muscles.

14. The reflexogenous zone is very diffuse in early infancy, and sometimes one is able to elicit a plantar reflex (either flexor or extensor) by stimulating a cutaneous area other than the sole, when stimulation of the sole fails to evoke a response.

PROTOCOLS OF CASES

Age 0 (At Birth) Normal Weight, 7 Pounds				
Case No.	Sex	Weight, Lbs.	Direction of Toe	Remarks
615	M	8	↑ each	Normal birth (Case 616, age 0-24 hours)
715	F	9¼	F	Forceps
716	F	3¾	E	6½ months' fetus
717	F	About normal	F	Reflex tried intra-uterinally and postnatally; transverse presentation; internal version under chloroform; baby born with two lower incisors
718	M	6½	F	Placenta praevia

Forceps, intra-uterine manipulation and placenta praevia did not produce a Babinski phenomenon, but prematurity did.

Age, 0-24 Hours

Case No.	Sex	Weight, Lbs.	Direction of Toe	Remarks
616	M	8	E (at 1 hr.)	Age = 1 hour; same case at birth was V (Case 615)
614	M	8	F (at 14 hrs.)	This infant died suddenly at the age of 25 hours (see notes, postmortem report and microscopic report of cord sections, p. 9)
605	F	6	F (at 22 hrs.)	

Age, 1-2 Days

614	M	8	V	Age = 28 hours; see Case 614 under 0-24 hours
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Age, 3 Days

602	F	10	F	Difficult forceps labor; hematoma of neck and contusion of face; convulsions on second day; mother suffered from dropsy for a few weeks before confinement
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Forceps and trauma of birth, as well as convulsions on second day did not produce a Babinski sign.

Age, 5 Days *

Case No.	Sex	Weight, Lbs.	Length, In.	Temperature	Cephalic Index	Direction of Toe	Feeding
729	M	3.15	16½	95.2	87	F	Bottle
730	M	3.11	17	95.2	81	E	Bottle

* These two babies were twins. They were prematurely born at 7½ months. Mother suffered from puerperal sepsis. In spite of the identical sex and prenatal as well as neonatal environments, etc., the plantar reflex was flexor in one and extensor in the other.

Age, 1-2 Weeks

Case No.	Sex	Weight, Lbs.	Direction of Toe	Remarks
606	F	8	F	Age, 11 days
607	F	4	E	Age, 12 days

Explanation of abbreviations and symbols: Under sex, M=male; F=female. Under direction of toe, F=plantar flexion (flexion); E=dorsiflexion (extension); V=variable (different either on the two sides or on the same side at different times);

↑=dorsiflexion; ↓=plantar flexion; o=no reflex.

↑ R = dorsiflexion on right side, plantar flexion on left side.

↑ L = dorsiflexion on left side, plantar flexion on right side.

↑ R = absent reflex on right side, dorsiflexion on left side.

↑ L = absent reflex on left side, dorsiflexion on right side.

↓ R = absent reflex on right side, plantar flexion on left side.

↓ L = absent reflex on left side, plantar flexion on right side.

v ↑ ↓ each = variable on each side.

PROTOCOLS OF CASES

Age, 2 Weeks; Normal Weight, 7½ Pounds, and Length, 20 Inches									
Case	Sex	Complaint	Wt., Lbs.	Length, Inches	Temp.	C. I.	Feeding	Toe	Remarks
4	M	Icterus, neonatorum	6.13	18½	96.4	72.7	?	E	
166	F	Uric acid calculus	6.0	19¾	96	72.2	?	F	
220	F	Tongue tie	6.15	21	98	82.6	?	F	
505	F	Wasting	2.12	17	97	75	?	↑ R ↓ L	Prematurely born at 8 months
683	F	Screaming	7.2	21	96.4	Breast	F	
751	M	2.4	98	80	Bottle	E	7 months' fetus; weight at birth, 3½ pounds
761a	F	Crying	8	Bottle	F	
35	F	Spina bifida	4.14	16	72	Breast	E	Eighth infant, full term
Age, 2-3 Weeks									
285	M	Flatulence	6.15	19	97	75	Breast	F	Age, 16 days
609	M	Nil	6.14	98.4	Breast	F	Forceps delivery; age, 17 days
609	M	Nil	6.8	Breast	E	Age, 19 days
789	M	Crying	8	98.4	Bottle	F	Age, 18 days
Age, 3 Weeks									
213	M	Ophthalmia neonatorum	5.1	17¾	97	88	Bottle	F	Mother consump- tive
244	M	Diarrhea	Very tiny infant				Bottle	E	Very feeble, puny infant; col- lapsed; brandy and oxygen given; premature
276	M	"Always hungry"	8	21¼	98.4	80	Breast	F	
655	M	Flatulence	7.12	22	98	Breast	V ↑ L ↓ R	
658	M	Swollen feet	9.3	22½	99	68	Breast	V ↑ R ↓ L	? Idiopathic dropsy
481	M	Vomiting	7.14	23¾	100.2	80	Bottle	F	
Age, 4 Weeks; Normal Weight, 7¾ Pounds; Length, 20½ Inches									
128	M	Wasting	5.3	26	98.4	85	Bottle	V ↑ R ↓ L	This was a baby with congenital absence of fibula and tarsal bones; curvature of tibia; see notes roentgen ray re- port, postmor- tem report and notes on sections of card, p. 9
258	?	Wasting	8	19	96.2	76	?	E	7 months' fetus
299	M	Vomiting	7.7	21	97.8	84	?	F	
335	M	Erythema	10.8	22	98.4	77	?	F	
329	M	Right inguinal hernia	4.9	17	96	75	Bottle	E	7½ months' fetus
375	F	Flatulence	6.8	19	98.2	75	?	F	
423	M	Wasting	4.6	16¼	96	79	?	F	Weight at birth, 5 pounds; ? full term
453	M	Phimosis	9.8	21¾	98.2	70	?	F	
470	M	Flatulence	10.8	24½	98	77	?	F	
581	F	Screaming	8.12	21	98	84	Breast	E	
610	M	Nil	7.14	Breast	F	
711	M	Rash on head	8.3	25	98.4	Breast	F	
Age, 5 Weeks									
132	F	Wasting, con- genital syphilis	6.1	18¼	98.2	80	F	
148	F	Wasting	7.13	20½	97.6	93	F	
167	M	Diarrhea and vomiting, wasting	7.2	20½	99.6	70	F	
183	F	Rash, (?) toxic	8.11	20½	98.4	79	E	Infant asleep
305	F	Fretful	6.2	18¾	97	75	F	
307	M	Vomiting	6.2	18½	96	75	F	
449	M	Sore buttocks	9.6	19¾	98.8	76	F	
458	M	Snuffles and nasal obstruction	11.3	22½	98.4	72.7	F	
603	F	Vomiting	7.7	18½	Bottle	F	Weight at birth, 4 pounds; prema- ture; breast fed only one day

PROTOCOLS OF CASES

Age, 5 Weeks—(Continued)									
Case	Sex	Complaint	Wt., Lbs.	Length, Inches	Temp.	C. I.	Feeding	Toe	Remarks
611	M	10	F	
631	M	Constipation	8.12	23½	99	76	Bottle	V	Breast fed first 2 weeks
703	M	Constipation	9.5	22	97.4	Breast	V	
704	M	Screaming	11.8	22	97	Breast	F	
739	F	Wasting	5.9	18½	96.2	77.7	Breast	E	8 months' fetus weaned at one month
Age, 6 Weeks									
12	F	Diarrhea and	8.10	21½	98.6	76	F	
275	F	Nil	8.8	21	97.4	80	F	
279	M	Wasting	6.15	21	98	80	V ↑ L R	
282	F	Bronchitis	12.12	23¾	97.4	81.8	F	
292	F	Flatulence	9.8	20¾	99	77	F	
322	M	Constipation	8.2	22	97	71.4	F	One of twins
341	F	Bronchitis	6.11	19½	96	76	F	
456	M	Screaming	9.9	20½	97.2	77	F	
461	F	Umbilical hernia	7.4	20	97	80	Bottle	F	Congenital syphilis; on breast 2 weeks
463	M	Systolic bruit all over heart	7.9	20½	98.4	80	Breast	F	(?) patent foramen ovale
582	F	Vomiting 10 days	8.15	21¼	98	84	Breast	E	
640a	F	Nil	Bottle	F	Same case as 602 (see under 3 days)
712	M	Right inguinal hernia	9.11	23½	98.4	72.7	Breast	F	
713	F	Flatulence	11.4	23½	98.2	81	Breast	E	
666	F	Wasting and vomiting	3.11	17	98.8	77.7	Bottle	F	7 months' fetus
678	?	F	See also same case under 1 yr. (681)
681	?	80	F	See also under 1 year = V
752	M	Nil	9	21½	Breast	F	
Age, 7 Weeks									
242	M	Wasting	8.5	22	96	76	F	
345	M	Rash, (?) toxic	10.12	21	97	77	V ↑ L R	
375	F	Flatulence	6.8	19	98.2	75	Bottle	F	Breast 3 weeks
425	M	Screaming	7.6	20	97	82.6	F	
445	F	Vomiting	7.5	22	98.4	84	F	
446	F	Constipation	6.12	19¾	96.6	80	F	
482	F	Thrush	12	21	98	77	F	
653	M	Glands in neck (?) C. S.	10.15	23¼	99.2	Breast	V ↑ L R	
662	M	Malnutrition	7.4	23½	98	77	Breast	V ↑ L R	
706	F	Wasting	5.14	19½	96	Bottle	V ↑ L R	
707	M	Umbilical hernia	9.4	21½	98.8	Breast	F	
733	M	Screaming	10.13	22½	98.2	82	Breast	F	
762	F	Screaming	Well developed				Breast	F	
Age, 2 Months (8 weeks); Normal weight, 9½ Pounds; Length, 21 Inches									
1	M	Wasting and diarrhea	9.6	21½	98.4	73	F	
13	F	Vomiting	11.2	20¾	99.8	96	Bottle	F	Breast 2 weeks
109	M	Wasting and diarrhea	9.8	21½	98.4	73	F	Twelfth infant
129	M	Bronchopneumonia	11.10	23	102	86	F	
142	M	Wasting and vomiting	7.7	21	97	79	F	
163	F	Wasting and diarrhea	7.0	19½	98	80	F	
170	F	Flatulence	9.6	23	99	79	F	
172	M	(?) C. S.	8.5	22	97.6	80	F	
334	F	Vomiting	9.10	21½	97.6	77	F	
174	M	Fretful and wasting	7.4	21½	97	76	F	
194	M	Wasting	7.10	21¼	98	84	Breast	V ↑	each
223	F	Adenoids	9.4	21¾	98	81	F	

PROTOCOLS OF CASES

Age, 2 Months (8 weeks); Normal Weight, 9½ Pounds; Length, 21 Inches—(Continued)

Case	Sex	Complaint	Wt., Lbs.	Length, Inches	Temp.	C. I.	Feeding	Toe	Remarks
339	M	Icterus neo-natorum	7.5	20	97.2	76	F	7 months' fetus
289	M	16	97.4	84	V ↑ L ↓ R	
388	F	Wasting	6	19½	96	76	F	
417	M	Bronchitis	9.4	22	97	80	F	Father and paternal aunt died of consumption, maternal uncle suffering from consumption
428	F	Wasting and vomiting	6.2	20	99.6	79	F	
430	F	Constipation	10.6	22½	97.6	76	F	
436	F	Rash	10.12	21¾	97	73	F	
447	F	Flatulence	9.8	20½	98	81	F	
457	F	(?) C. S.	5.4	20	97.4	79	F	
460	F	Not progressing	7.7	21	97	80	F	
459	F	Constipation	13.1	22½	99.2	81	F	
469	M	Wasting	7.12	19¼	98	76	F	
487	F	Wasting	4.7	17	96.6	79	F	} Premature twins } at 8 months
488	M	Cough	5.5	18	98	75	F	
626	F	Vomiting and crying	7.1	20	98	F	
638	F	Snuffles	8.12	20½	97	Breast	E	
639	M	Constipation	7.15	21	97.2	Breast	E	
677	F	Umbilical hernia	9.13	24	97.4	Breast	F	
708	M	Umbilical hernia and double inguinal hernia	10.8	21½	98	Bottle	F	Breast fed 3 weeks
712	M	Inguinal hernia	9.11	23½	98.4	73	F	
740	F	Wasting	7.15	22¼	99	81	Breast	E	
743	M	Wasting and vomiting	8.3	21	98.2	82	Bottle	F	Breast fed 2 weeks
Age, 9 Weeks									
432	?	Wasting, flatulence	7.1	21½	97.2	72.7	V ↑ L ↓ R	Same case as 432a; under 6 mos. = F
318	M	Phimosi	8.13	21½	97.8	77	F	
673	F	Wasting	6.6	19	98	75	F	
593	M	Inguinal hernia	9.0	20	98.4	81	V ↑ L ↓ R	8 months' fetus
477	F	Screaming	6.10	20½	97	76.2	F	One of twins
737	F	(?) C. S.	8.0	22	97.2	76.2	Breast	E	
Age, 10 Weeks									
208	F	(?) Pertussis and wasting	9.14	23½	97.4	80	E	
226	F	Bronchitis	8.4	20½	98	90	F	
312	F	Wasting	7.3	20	96.4	71	F	
431	F	Cough	8.6	20	97	76.2	E	
325	F	Vomiting	10.15	22	98.4	72.7	F	
452	M	Rectal prolapse	11.1	20½	99.6	72.7	F	
600	M	Wasting	4.9	17	97	79	F	} Twins; premature; fifth pregnancy
601	M	Wasting	5.10	18¼	97.8	95	F	
629	M	Constipation	10.8	23½	98.4	82.6	Breast	F	
643	M	Wasting	8	20	96.6	79	Bottle	E	Breast 2 weeks
644	F	11.7	23	98	76	Breast	E	
659	M	Vomiting	11.10	23¾	99	Breast	V ↑ L ↓ R	
661	M	Malnutrition	7.8	22½	97.6	Breast	F	
684	M	Wasting	6.2	20½	98	79	Breast	E	
637	F	Wasting	5.13	18¾	97	Bottle	F	
744	M	Screaming	8.2	24½	98	85	Bottle	E	Breast 2 weeks
761	F	Wasting	7.12	Bottle	F	
Age, 11 Weeks									
151	M	Wasting	7.4	20½	99	72.7	Breast	F	
311	F	Wasting	12.8	23	99	76	E	
455	M	Wasting	6.15	18¾	98	76	F	Father had splenectomy 8 mos. previously; paternal uncle had pernicious anemia
633	M	Constipation	11.2	23¾	97	Breast	E	
650	M	Wasting	6.5	20	97.2	Bottle	V ↑ L ↓ R	} Twins; premature
651	M	Wasting	6.11	20	97.6	Bottle	E	
768	M	Wasting	8	19½	96	70	Breast	E	

PROTOCOLS OF CASES

Age, 3 Months; Normal Weight, 11 Pounds; Length, 22 Inches									
Case	Sex	Complaint	Wt., Lbs.	Length, Inches	Temp.	C. I.	Feeding	Toe	Remarks
8	M	(?) Toxic poisoning	12.5	25	98.4	78	F	
14	M	Wasting	7.10	21½	97	80	F	
24	F	Anemia and wasting	6.15	20½	97.4	81	F	
26	M	Wasting	8.15	21	98.6	76.2	F	8 months' fetus
57	F	Sore buttocks	10.12	22¼	96	86	E	
68	M	Flatulence	8.13	20	98.4	86	F	
93	F	Constipation	11.7	23½	97	77	F	8 months' fetus
98	M	Losing weight	8.15	22¼	98	82	F	Thirteenth infant; six died of wasting, one died of meningitis
112	F	Anemia	6.15	20½	97	81	F	
119	M	Cough	8.13	22	97	76	F	
136	M	Wasting	7.4	22	97	73	F	
144	M	Rash (?) toxic	12.6	24	98.2	74	V O L ↓ R	
158	M	Wasting	9.4	23¾	103	71	F	
165	M	Wasting	8.7	22½	98.2	81	F	
168	M	Vomiting and screaming	11.5	23	97.2	81	V ↑ ↓ R	each
178	M	Diarrhea and vomiting	9.13	22½	96.6	74	V ↑ L ↓ R	
186	M	Skin eruption	9.5	22	98.8	86	F	
204	F	Erythema	10.11	21½	97	77	F	
256	M	Constipation, sleeplessness	8.13	21¾	97.6	71	E	
266	M	Wasting	11.1	23	98.4	74	F	
304	M	Constipation	11.14	21¾	98	86	F	
319	M	Diarrhea and vomiting	12.10	25	97.2	77	F	
401	M	Cough	11.4	21½	100.4	70	F	
419	F	Cough	15.4	21½	98	73	F	
437	M	Wasting	8.4	20½	98.4	81	E	
440	F	Wasting	8.13	20½	97	73	F	
484	F	Wasting	6.0	19	98	70	F	8 months' fetus
493	M	Wasting	6.10	19¼	96.2	76	E	
545	M	Flatulence	8.4	21	97.2	76	Breast	F	
598	F	Malnutrition	7.7	19½	97.2	76	V ↑ L ↓ R	
619	M	Screaming	Bottle	E	"Glaxo" baby
620	F	Nil	9.12	22¼	97.4	86	Breast	E	
635	F	Cough	11.7	24	98.8	77	Breast	E	
640	M	Cough	E	Congenital hydrocephalus
664	F	Wasting	7.4	22¾	98.8	81	Bottle	F	
676	M	Wasting, C. S.	5.5	18¼	96.6	Bottle	F	Premature (9 mos.); breast fed 2 weeks
700	F	Rash on thigh	13.7	24¼	99.2	Breast	E	
652	F	Supernumerary thumb	12.2	22¾	98.2	Breast	E	
728	F	Umbilical hernia, wasting	7.10	24	96	84	Bottle	V ↑ R ↓ L	
742	M	Wasting	6.15	23	98.4	85	Breast	V ↑ L ↓ R	
333	M	Wasting	9.10	21½	100.4	70	F	
670	M	Wasting	7.2	23	97	76	Bottle	F	
Age, 14 Weeks									
130	M	Wasting	7.9	20¼	97.4	76	F	
274	M	Diarrhea and vomiting	14.3	25	98	90	F	
421	M	Wasting	8.13	21½	97	78	Breast	F	
590	M	Umbilical hernia	9.11	22	98.4	76	Bottle	F	
654	F	Screaming	11.13	24	99.6	Breast	V ↑ L ↓ R	
667	M	Wasting	11.1	23	98.4	74	Breast	F	
685	F	Constipation	12.2	26	99.2	Breast	F	
624	M	Wasting	7.10	19	96	V ↑ L ↓ R	
Age, 4 Months; Normal Weight, 12½ Pounds; Length, 23 Inches									
5	F	Wasting and vomiting	8.9	19	97.2	76	V ↑ L ↓ R	
11	F	Diarrhea and vomiting	12.8	24	96.6	79	F	
90	M	Wasting and vomiting	10.4	22½	97	79	F	

PROTOCOLS OF CASES

Age, 4 Months— Normal Weight, 12½ Pounds; Length, 23 Inches—(Continued)									
Case	Sex	Complaint	Wt., Lbs.	Length, Inches	Temp.	C. I.	Feeding	Toe	Remarks
106	F	Not gaining	8.9	19½	98.2	78	V ↑ L ↓ R	
140	M	Left apical pneumonia with convulsions	9.5	21	103	81	V ↑ R ↓ L	
160	M	Bronchitis	16.13	25½	96.6	82	F	
164	M	Diarrhea and vomiting, wasting	11.15	24½	96	85	V ↑ R ↓ L	
173	F	Malnutrition	8.14	98.6	80	F	
175	F	Intestinal toxemia	9.2	21½	98.4	81	E	8 months' fetus
254	M	Wasting and diarrhea	10.9	22	97.4	86	F	
287	M	Ectopic vesicæ	14.8	23	100	79	F	
320	M	Seborrhea capitis, (?) imbecility	10.8	24½	98	73	F	
323	M	Malnutrition	7.1	98.2	73	F	Premature
370	M	Wasting	8.12	24	101.8	83	F	
408	M	Eczema; right inguinal hernia	13.6	23¾	97	79	V ↑ R ↓ L	
473	F	Umbilical hernia, bronchitis	10.3	20½	99	76	F	
604	F	Pertussis	Well developed	Breast	F	
622	M	Vomiting	E	
672	F	12.10	24½	98.6	81	Breast	E	
674	M	Umbilical	10.7	22	98	Bottle	E	} Twins, each breast-fed 1 month 8½ months' fetus Breast fed 2 weeks
675	F	hernia	12.2	23¾	98.2	Bottle	F	
684	M	Wasting	10.8	23½	99.2	E	
701	M	Wasting	10.14	23	97	Bottle	F	
422	M	Right inguinal hernia	9.9	21	97.8	73	F	
599	F	Wasting	8.11	20	97.4	77	E	
719	F	Slight hypertrophy of right side of face	16.8	26	98.4	Bottle	F	
265	M	11.7	22	98	83	Breast	F	
306	M	Diarrhea	11.4	23½	99	79	F	
741	F	Constipation	7.13	23½	98	76	Breast	E	
748	F	Screaming	10.4	25¼	97	90	Bottle	E	Breast fed 3 weeks
Age, 5 Months; Normal Weight, 14 Pounds; Length, 23½ Inches									
27	F	(?) Pertussis	11.6	23½	99	70	F	
33	M	Wasting	9.9	22¼	97.2	81	V ↑ L ↓ R	
84	F	Wasting and bronchitis	11.2	26	97	75	F	
105	F	Bronchitis	11.6	23½	99	70	F	3 weeks premature
146	M	Diarrhea and vomiting, wasting	12	24	97.6	82	F	
155	?	Diarrhea	15.6	27	98	86	F	
162	M	Wasting	8.9	21½	96	85	V ↓	each
235	M	Wasting, pulmonary tuberculosis	8.0	25	97	74	F	
283	F	Restlessness at night	13	24¾	99	83	F	
324	F	Vomiting	7.4	20	96	71	E	
412	F	Slight mongolism	11.2	21½	99	85	F	
315	M	Bronchitis	Well developed	F	
427	M	(?) Defective sight	15.4	27½	98	79	F	
441	F	Digestive trouble	9.3	19¾	98	77	F	
450	F	Wasting	13	23¼	98	76	F	
458	M	Snuffles	11.3	22½	98.4	73	F	
642	M	Cough	15.11	26	98	79	Breast	V ↑ L ↓ R	
732	F	Wasting	9.13	24¼	98.2	82	Bottle	V ↑ R ↓ L	Breast fed 2 mos.
763	F	Nil	17.4	Bottle	E	Same case as 719 under 4 mos. = F
Age, 6 Months: Normal Weight, 15 Pounds; Length, 24 Inches									
2	F	Bronchitis	6.15	25	97	78	F	
15	M	Diarrhea and vomiting, internal strabismus (due to error of refraction)	9.2	22¾	97.6	83	F	

PROTOCOLS OF CASES

Age, 6 Months; Normal Weight, 15 Pounds; Length, 24 Inches—(Continued)									
Case	Sex	Complaint	Wt., Lbs.	Length, Inches	Temp.	C. I.	Feeding	Toe	Remarks
108	F	Bronchitis	16.5	25	97	74	F	
153	M	Wasting, diarrhea and vomiting	10.13	23	97.4	81	F	
176	M	Diarrhea and vomiting	11.12	24	98.4	85	F	Twins, 6 weeks premature
177	M	Diarrhea and vomiting	8	21	98.6	77	F	
201	M	Diarrhea	16.2	21½	99	87	F	
300	M	Vomiting	15.11	27	98.8	80	F	
389	F	Fatulence and cough	16.1	23½	97.8	80	F	
390	M	Restlessness	17.12	25	99	80	V ↑ L ↓ R	7 weeks premature
400	M	Diarrhea	14.6	24	99	81	F	
442	M	Diarrhea and vomiting	14.11	25½	99.2	78	F	
426	M	Diarrhea and vomiting	16.13	26	98.6	83	F	
485	F	Rectal prolapse	F	
397a	F	F	
432a	?	F	Same case as 432 under 9 wks. = V
141	M	(?) Meningitis; fontanel bulging; (?) hydrocephalus	12.1	25	97.6	88	F	
634	M	Wasting	7.6	23½	97.4	Breast	F	
665	M	Wasting	14.8	24	99	73	Breast	V ↑ L ↓ R	
594	M	16.0	26	98.8	88	F	
667	F	Diarrhea and vomiting	11.7	22½	97.8	82	Breast	V ↑ L ↓ R	
731	F	Wasting	7.4	22	98	82	Bottle	V ↑ L ↓ R	
735	M	Screaming	9.3	21½	98	85	Bottle	F	
Age, 7 months; Normal Weight, 16 Pounds; Length, 24½ Inches									
82	M	Not thriving	13.8	23	99.6	83	E	6 weeks premature, 4 lbs. at birth
95	M	Impetigo	15.2	25¼	97	87	F	
161	F	Wasting	12.10	24	97.4	77	F	
230	F	Rickets	12.5	24¼	98	78	F	
281a	F	Well developed	F	
338	M	Rickets	18.9	28	98	80	F	
357	M	Convulsions	15.14	28	98.2	83	F	
586	M	Diarrhea and vomiting	15.13	26	98.4	75	Breast	F	8 months' fetus
591	F	Malnutrition	7.3	18¾	99	73	Breast	F	
596	M	19.12	25½	99.2	75	F	
623	M	Convulsions	9.5	97.2	F	
656	M	Seborrhea capitis	17.11	26	98	Breast	F	Age, 7½ months
738	M	Wasting and vomiting	10.5	22½	97.8	77	Bottle	V ↑ R ↓ L	6½ months' fetus; breast fed 6 wks.
745	F	Wasting and vomiting	8.4	22½	96	83	Breast	V ↑ L ↓ R	During sleep Twins
746	M	Wasting and vomiting	9.6	21¾	97.4	74	Breast	F	
749	M	Diarrhea	9.3	20½	97.4	87	Bottle	V ↑ R ↓ L	
Age, 8 Months; Normal Weight, 17 Pounds; Length, 25 Inches									
7	M	Diarrhea and vomiting	13.7	26¾	99	79	F	
139	F	Wasting	8.3	22	98.4	83	F	
149	M	Diarrhea and vomiting	8.12	23	97	82	V ↑ R ↓ L	
225	F	Diarrhea	16.4	25½	99.2	85	V ↑ L ↓ R	each
234	F	Injury to leg; no fracture	20.2	28½	99	90	F	
255	M	Mongolism; slight macroglossia; nystagmus; adenoids	9.7	26¾	98	83	V	
406	M	Cough	17.5	28	99.6	80	V ↑ L ↓ R	
451	F	Cough	16.12	27	99.4	76	F	
485	M	Diarrhea	18.10	28½	100.6	79	Bottle	F	7 months' fetus; family history of tuberculosis; breast fed 2 wks.
413	F	86	E	
690	F	Malnutrition	11.4	24	98	Breast	V ↑ L ↓ R	Age, 8½ months
632	M	Wasting	11.0	24	98	90	Breast	F	8 months' fetus
747	F	Bronehitis	20.3	31	98.6	73	Breast	F	

PROTOCOLS OF CASES

Age, 9 Months; Normal Weight, 18 Pounds; Length, 25½ Inches									
Case	Sex	Complaint	Wt., Lbs.	Length, Inches	Temp.	C. I.	Feeding	Toe	Remarks
185	M	Diarrhea	20.4	28½	97	84.6	E	
206	M	Restlessness	21.4	32½	101.4	87	F	
211	M	Ileocolitis	11.4	20¾	100.2	85.7	F	
259	M	Cough	13.7	24½	99.2	78	F	
294	M	Eczema	16.3	29	97.2	80	F	
310	F	Wasting	11.2	27	97	82.6	F	
627	M	Malnutrition	11.9	23½	98.4	91	Breast	E	} 8 months' twins; } age 9½ months
628	M		11.13	26	99	82.6	Breast	E	
433	M	Diarrhea and vomiting	10.6	22	97	73.7	F	7 months' fetus
Age, 10 Months; Normal Weight, 19 Pounds; Length, 26 Inches									
6	F	Bronchopneumonia	15.13	27	101.2	79	F	
291	F	Diarrhea	17.11	27	97	85	F	8 months' fetus
309	F	Rickets	12.10	25½	98.4	83	Bottle	F	
630	M	Cough	11.2	23¾	98.6	82	Bottle	F	
709	M	Diarrhea and vomiting	14	25	98.2	Bottle	F	
436	F	80	F	
314	F	Diarrhea	17.7	27	98	74	F	8 months' fetus; one of twins
476	F	Ileocolitis	10.14	98	82	F	
Age, 11 Months; Normal Weight, 20 Pounds; Length, 26½ Inches									
22	M	Rickets	11.7	24¾	79	F	
138	F	Convulsions	22.7	29½	96.4	83	F	Strong family history of tuberculosis Breast 3 months
157	M	Bronchopneumonia; (?) tuberculosis	15.2	27	99.2	79	Bottle	F	
263	F	Otorrhea and eczema	21.10	29½	97.2	83	V ↑ R ↓ L	
649	M	Diarrhea and vomiting	20.3	29	97.4	Breast	V ↑ R ↓ L	On breast 9 mos. Breast 3 weeks
705	M	Screaming	16.8	26½	99	Bottle	E	
23	F	Bronchitis	16.3	27½	97.8	76	F	
688	?	Coryza	9.10	96.4	87	Bottle	F	Breast 1 month; age, 11½ months
454	M	Screaming	19.8	27½	96.2	79	F	
758	M	Second degree of scalds of leg and thigh (left)		Well developed			Bottle	V ↑ R ↓ L	
Age, 1 Year; Normal Weight, 21 Pounds; Length, 27 Inches									
199	F	Scabies	17.15	27	97	79	E	
583	?	Wasting	19	28½	99.8	83	Bottle	V ↑ R ↓ L	Breast, 2 months Breast fed 2 weeks (see also under 6 weeks F)
678	?	15.13	98.4	80	Bottle	F	
681	?	17.15	98	83	Breast	V ↑ each ↓	During sleep (see also under 6 wks. F)
765	M	External strabismus due to myopia	Normal development				Breast	F	
Age, 1 Year 1 Month; Normal Weight, 22 Pounds									
13a	M	Wasting; phthisis	17	29½	98.4	74	F	
16	F	Wasting	15.10	25	103.8	83	F	
232	F	Wasting	14.4	29	98.4	80	F	
368	M	Wasting	14.10	25½	98.8	82	V ↑ R ↓ L	
434	F	Bronchitis	21.4	23¾	97.8	80	F	
602	F	Screaming	?	?	?	?	V ↑ each ↓	Fortnight premature; mother suffered from albuminuria of pregnancy
621	F	Nil	19.12	31	97.2	91	Breast	V ↑ R ↓ L	
637	F	Screaming and wasting	10.13	23½	97.2	Bottle	E	Breast fed 5 weeks
646	F	Diarrhea and vomiting	18.6	29½	97.4	Breast	E	

PROTOCOLS OF CASES

Age, 1 Year 1 Month; Normal Weight, 22 Pounds—(Continued)									
Case	Sex	Complaint	Wt., Lbs.	Length, Inches	Temp.	C. I.	Feeding	Toe	Remarks
648	F	Diarrhea and vomiting	18.6	29½	97.4	E	
652	F	Supernumerary thumb, right hand	12.2	22	98	E	
700	F	Umbilical hernia	20.0	30½	99.2	Breast	E	During sleep
Age, 1 Year 2 Months; Normal Weight, 22½ Pounds									
336	F	Umbilical hernia	21.8	29	98.4	80	F	
354	M	Wasting	15.8	27	99.6	79	E	
467	?	Rickets	16.9	29½	98.4	83	F	
472	M	Bronchopneumonia	23.10	102.2	85	F	
595	M	16.3	26	99.4	70	F	During sleep
714	F	Umbilical hernia; convulsions when 6 weeks old	20	29	98.6	87	Breast	V ↑ ↓ L R	During sleep; breast fed 10 months
Age, 1 Year 3 Months									
137	F	Weakness of neck muscles; (?) slight imbecility	17.4	26	99	77	F	
189	F	Loss of appetite	18.12	98.2	77	F	
260	M	Intestinal toxemia	12.2	22½	98	82	F	
504	M	Phimosis; right and left inguinal hernia	21.4	33½	97.6	80	F	
Age, 1 Year 4 Months									
396	M	Bronchitis and wasting	14.8	23½	98.6	80	F	
489	M	(?) tuberculosis peritonitis	16.5	27½	98	87	F	
736	F	Refusing food	20.11	30½	102	83	Bottle	F	Breast fed 6 weeks
Age, 1 Year 5 Months									
381	F	Abscess of buttock	18.12	27	98.8	87	V ↑ ↓ L R	8 months' fetus
587	M	Measles	17.10	23½	99	80	Breast	V ↑ ↓ L R	
589	F	Otorrhea	16.12	28½	99.2	83	Bottle	E	
Age, 1 Year 6 Months									
17	M	Diarrhea and vomiting	14.8	29	100	83	F	
18	M	Diarrhea; adenoids; perforation of right membrana tympani; anemia	18.7	31	98	80	Breast	F	
131	M	Eczema	19.10	31½	98	83	F	
592	F	20.15	29	98.4	77	Breast	E	
597	F	Malnutrition	16.15	27	98.2	70	F	
671	M	Bronchopneumonia	18.5	31	99	87	F	
Age, 1 Year 7 Months									
76	M	Wasting; (?) tuberculosis	18.9	30¾	97	77	F	Family history of tuberculosis
195	M	Wasting; (?) tuberculosis	32	98.6	84	V ↑ ↓ L R	
435	M	Scabies	20.1	30	97.4	75	F	Hydrocephalus
Age, 1 Year 8 Months									
313	F	Pertussis	18.4	30	98.8	78	F	
480	M	Pertussis	32	99.4	80	F	
420	F	Bronchitis	24.2	28¾	97.8	78	F	
Age, 1 Year 9 Months									
94	F	Not taking well	22.10	32½	99	80	F	
196	F	Well developed	87	F	
278	M	Slight bronchitis	20.4	31	98	84	F	
625	M	E	

PROTOCOLS OF CASES

Age, 1 year 10 Months								
Case	Sex	Complaint	Wt., Lbs.	Length, Inches	Temp.	C. I.	Feeding	Toe
218	M	F
382	F	Congenital im- becility; no his- tory of fits or imbecility in family	15.15	24½	99.2	79	E
721	F	Bronchopneu- monia; pertussis	Well developed	102.2	E

Age, 1 Year 11 Months								
Case	Sex	Complaint	Wt., Lbs.	Length, Inches	Temp.	C. I.	Toe	Remarks
37	F	Screaming	35½	98	84	F	
135	M	Wasting	13.4	26½	98.6	83	F	
492	M	Otorrhea	?	Well devel- oped		88	V	Breast fed 9 months; pneu- monia at 7 months
Age, 2 Years								
316	M	Malnutrition	18.12	98.4	87	F	
317	M	Debility and fretfulness	21.10	32½	97.8	78	F	8 months' fetus
346	M	Weakness of legs and ankles	34¾	98.4	81	F	
369	F	22.6	99.2	86	F	
546	?	Earsache and occasional right sided convulsions	23.4	34½	98.4	84	F	
640b	F	Bronchitis	Normal development				F	
Age, 2 Years 2 Months								
443	M	31	98	81	F	Ringworm
569	M	30	98	77.7	F	
Age, 2 Years 6 Months								
302	M	22.3	30	100	76	F	Pyrexia; child still unable to walk; no signs of ner- vous disease (e.g. paraly- sis, etc.)
402	M	37	97	75	F	
702	M	36	98.2	F	Breast baby
750	F	34½	98.2	V ↑ R ↓ L	Breast fed
Age, 2 Years 8 Months								
251	M	31¼	98.6	80	V ↑ R ↓ L	A case of petit mal; family history of fits; all reflexes normal, no Chvostek sign; intelligent infant; walked at 1 yr. 6 mo.; talked at 2 years
764	F	Scabies	F	Breast 1 year
Age, 2 Years 9 Months								
285a	M	23.1	30½	99.2	80	F	Left anterior poliomyelitis since 1 year old
640d	M	F	
Age, 2 Years 10 Months								
725	F	101	F	
Age, 2 Years 11 Months								
686	F	23.1	34½	98.4	80	V ↑ R ↓ L	Pulmonary tuberculosis; breast fed
241	M	97.6	77.7	F	Case of acute lymphatic leukemia*

* Differential blood count: polymorphonuclears, 9 per cent.; large lymphocytes, 71 per cent.; small lymphocytes, 7 per cent.; lymphoidocytes, 11 per cent.; myeloblasts, 2 per cent. Although from the point of view of the present investigation it has no special interest, it is a very instructive one from the general medical standpoint. The presence of lymphoidocytes in the blood is believed to point to an early fatal termination and, indeed, this child died suddenly within a couple of days after it was first seen by me.²²

PROTOCOLS OF CASES

Age, 3 Years									
Case	Sex	Complaint	Wt., Lbs.	Length, Inches	Temp.	C. I.	Toe	Remarks	
466	?	34	100.2	80	F	Adenoids	
640c	M	F		
722	F	98	F		
Age, 3 Years 4 Months									
415	M	Injury left ankle	V	↓ Left	↓ R Synovitis, (?) tuberculous
Age, 3 Years 5 Months									
766	F	Urticaria	Normal development				E	outer sole	F inner sole
Age, 3 Years 9 Months									
337	F	General debility	38¾	98	80	F	(?) Rheumatic soft systolic bruit at apex	
759	F	Pain left knee	E, F		
Age, 4 Years									
618	F	Pertussis	E	Convulsions at 11 a. m.; ob- servation of reflex at 8 p. m.	

Cases Over 4 Years

No.	Sex	Toe	Remarks
723	F	F	} Age 4½ years; myocarditis after diphtheria
724	F	F	
770	M	F	
764a	F	F	Age 4 years 8 months
602a	M	F	Age 4 years 10 months
617	M	F	Age 5 years
757a	M	V	Age 5 years 6 months
771	F	↓ R	Age 5 years 6 months
772	M	↓ L	Age 5 years 6 months
773	F	F	Age 6 years
775	F	F	Age 6½ years
774	F	F	Age 6 years 9 months
774	M	F	Age 6 years 9 months
753	M	E	Age 7 years 9 months
6 st. 4 ft. 6			Very typical Babinski phenomenon; complaint, walking on tip toes from infancy; age 9 years 4 months (see p.)
777	M	V	Age 6 years (same case as 617)
3 st. 2-3 ft. 6		↓ R	
		↓ L	

CAN YEAST BE USED AS A SOURCE OF THE ANTINEURITIC VITAMIN IN INFANT FEEDING? *

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The reports of Eddy and Roper ¹ and Daniels and Byfield ² on the effect of adding substances containing the antineuritic vitamin ³ to the diets of artificially fed infants suggests that at least part of the difficulty in feeding these babies is due to a too low concentration of the antineuritic vitamin in many of the feeding mixtures. Cow's milk has been shown to contain less of this vitamin than many other natural foods,⁴ the amount present being dependent on the vitamin content of the food of the cow, for it appears that "vitamins pass into the milk only as they are present in the diet of the mother."⁵ When cow's milk is diluted, a necessary procedure in feeding young babies, unless some antineuritic vitamin is added from other sources, too little may be present in the feeding mixtures. The baby who is well and able to take his normal quota of food appears to get enough of this particular growth material to meet his needs. But the young baby or the baby with disturbed digestion who cannot take the usual amount of food may fail to gain because the antineuritic vitamin content of the food falls below his minimal requirement.

Eddy and Roper found that a specially prepared powder, made from the alcoholic extract of the pancreatic gland of lambs, when added to the diet of marasmic infants, stimulated growth. Previous experiments on rats had demonstrated that this powder contained the antineuritic vitamin. Daniels and Byfield, working with well babies, observed that many who were not gaining on food mixtures containing adequate amounts of the well known food constituents—protein, fat, carbohydrate and inorganic salts—increased in weight when the antineuritic vitamin (obtained from wheat embryo) was added to the feeding mixtures. In many instances these children were receiving food mixtures supplying from 115 to 130 calories on their theoretical weights—considerably more

* Received for publication, Aug. 18, 1921.

* This study was made possible through the courtesy of the Pediatric Department of the College of Medicine of the University of Iowa.

1. Eddy, W. H., and Roper, J. C.: *Am. J. Dis. Child.* **14**:189 (Aug.) 1916.

2. Daniels, A. L., and Byfield, A. H.: *Am. J. Dis. Child.* **18**:546 (Dec.) 1919.

3. The term antineuritic vitamin is used throughout the report to indicate the growth promoting vitamin designated as "Water Soluble B" by McCollum and his co-workers.

4. Osborne, T. B., and Mendel, L. B.: *J. Biol. Chem.* **34**:573, 1918.

5. McCollum, E. T.; Simmonds, N., and Pitz, W.: *J. Biol. Chem.* **27**:33, 1916.

than is usually considered necessary. Growth in a number of instances continued until somewhat less than 100 calories per kilogram was being given. These observations suggest a possible explanation for the well known fact that the baby fed artificially needs more food than the breast fed baby.

In view of these findings it seems desirable to obtain some inexpensive, readily available source of this antineuric vitamin which may be added to the food of the very young infant or the baby who for one reason or another is unable to take a sufficient amount of food to ensure an adequate ingestion of the vitamin. Neither the wheat embryo extract used by Daniels and Byfield, nor the pancreas preparation of

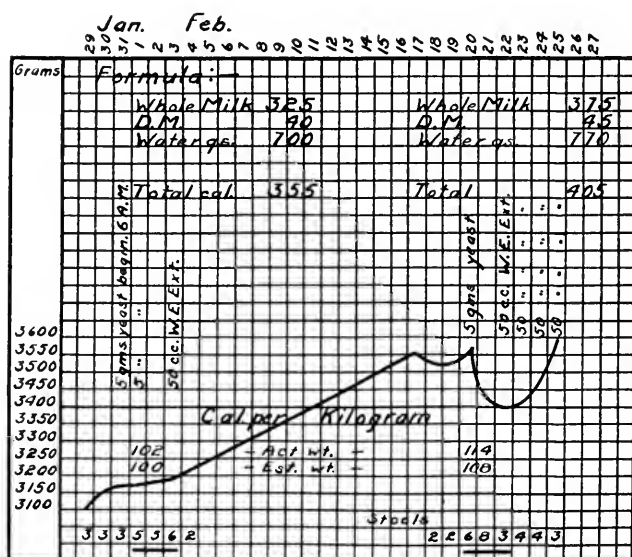


Fig. 1.—Sybil T.; born Dec. 21; birth weight, 2,858 gm.; aged, 1¼ months.

Eddy and Roper are easily available to the practitioner or the mother. The vegetable soup suggested⁶ by the former investigators as a source of the antineuritic vitamin has been used with much success for well babies over 4 months of age. It is, however, not well tolerated by the very young baby or the baby suffering from digestive disturbances. Both orange⁷ and tomato⁸ juice can be used as sources of the antineuritic vitamin, but considerably more must be used than is necessary to protect against scurvy; and the young baby or ill baby frequently cannot take enough to furnish the required amount.

6. Daniels, A. L., and Byfield, A. H.: loc. cit.

7. Byfield, A. H., and Daniels, A. L.: *Am. J. Dis. Child.* **19**:349 (April) 1920.

Osborne, T. B., and Mendel, L. B.: *J. Biol. Chem.* **42**:465, 1920.

8. Osborne, T. B., and Mendel, L. B.: *J. Biol. Chem.* **41**:451, 1920.

In animal experimentation yeast⁹ has been used with much success as a means of furnishing this growth promoting vitamin, its potency in this respect being considerably greater than that of many foods tested,¹⁰ especially milk.¹¹ Osborne and Mendel working with rats, observed that normal growth could be secured when 0.2 gm. per day was used as the only source of the vitamin, whereas 16 c.c. of milk was necessary to furnish an adequate amount. The possibility of using yeast as a means of increasing the antineuritic content of infants' food was suggested. The introduction of purin forming substances into the diets of infants did not commend itself, but since in all probability only a small amount of yeast would be needed to produce the desired results, it

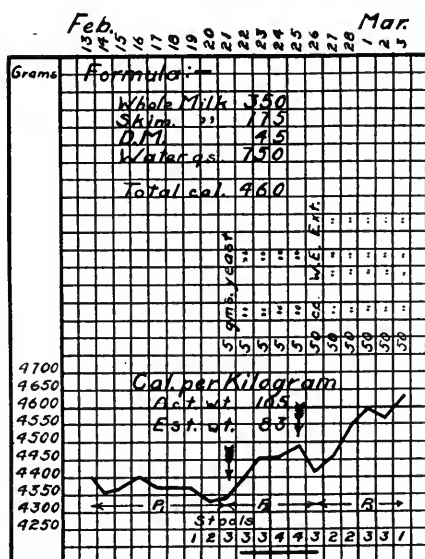


Fig. 2.—Clarice P.; born October 27; birth weight, 3,750 gm.; aged, 3½ months

was reasoned that the good which might accrue would perhaps outweigh the theoretical objection. In the investigation from 2 to 10 gm. air dried pulverized yeast (Fleischmann's) were soaked in a small amount of water, subsequently boiled and added to the day's feeding. In certain instances, when no gain in weight resulted from the yeast additions, wheat embryo extract (50 c.c.) was substituted for the yeast, in order to make sure that the failure to gain was not due to a lack of the antineuritic vitamin. In some cases the wheat embryo extract was added for therapeutic purposes.

9. Osborne, T. B., and Mendel, L. B.: J. Biol. Chem. **31**:149, 1917.

10. Osborne, T. B., and Mendel, L. B.: J. Biol. Chem. **32**:309, 1917.

11. Osborne, T. B., and Mendel, L. B.: J. Biol. Chem. **34**:537, 1918.

In determining the influence on growth of a given vitamin addition to the diet of infants, several factors must be considered. The babies under observation should be as nearly normal as possible—that is, there should be no elevated temperatures, diarrhea, or other indications of indigestion or illness. The amount of food given must be sufficient to cover the physiologic requirements for age and weight. The feedings must be prepared with the greatest accuracy, as to amount of materials used and method of preparation. Care must be taken to see that all the food is taken and retained. It is most desirable that a stationary weight period of at least four days on a satisfactory food mixture should precede the period during which the added material is given. The

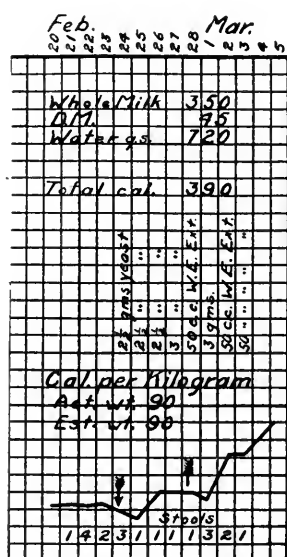


Fig. 3.—Keith M.; born December 27; birth weight, 3,595 gm.; age, 7 weeks.

character and number of the stools, both before and during the observation period, should be noted. If possible, the baby should be kept on the same formula, without the added vitamin, for four days following the period.

In testing the influence of yeast additions on growth, these methods, in so far as possible, were followed. The sixteen babies used for the observations, with the exception of two suffering from sudamina, were normal healthy babies from 5 weeks to 6 months of age. Details of the feeding mixtures, weights, etc., in a number of the more typical cases are given in the accompanying charts.

The most noticeable general effects of the yeast additions, especially with the younger babies, was the change in the number and character of the stools, a formed "safe" stool often becoming diarrheal. In many

instances not only was the character of the stool changed, but the number per day was greatly increased even when comparatively small amounts of yeast were used. These frequent diarrheal stools were in a number of cases followed by sudden losses in weight. The results were sometimes so disastrous that it was necessary to institute corrective measures at once. For example, the addition of 5 gm. dried yeast (equivalent to about two-thirds of a fresh yeast cake) to the feedings of Sybil T., a 6 weeks old baby, was followed by frequent watery stools. After three feedings (twelve hours) it was necessary to change to an "eiweiss" milk formula to check the diarrhea. Three weeks later the yeast additions were again tested with results that were even more

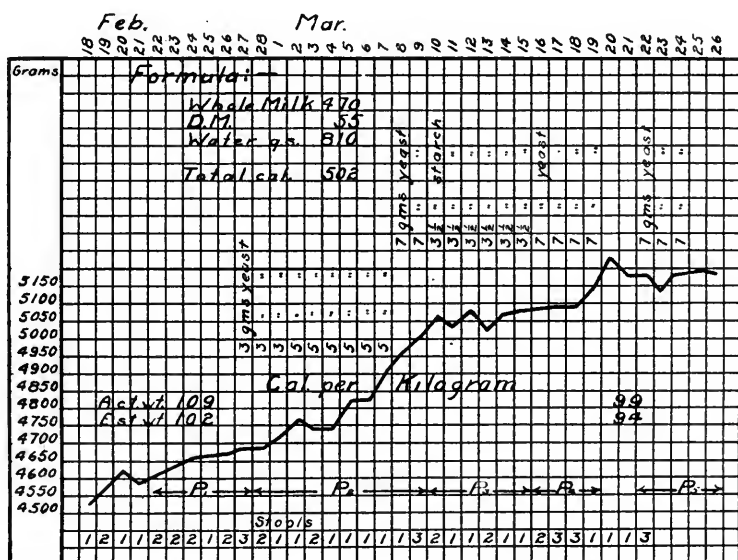


Fig. 4.—Gretchen S.; born Nov. 30, 1920; birth weight, 3,396 gm.; age, 2½ months.

marked than during the first yeast period. At this time the feedings were not well retained, and the stools increased from two per day to six and eight, respectively. There was a sudden loss in weight, and after a twenty-four hour trial the baby was returned to its previous formula to which were added 50 c.c. of our wheat embryo extract.

The addition of 5, 7 and 21½ gm. yeast to Robert L.'s feedings produced somewhat similar results—marked diarrhea and loss in weight when the larger amounts of yeast were used. With the smaller amount of yeast—21½ gm.—the stools were less frequent and formed, but apparently not enough of the antineuritic vitamin had been added with this small amount of yeast to produce any apparent physiologic effect; the subsequent addition of 50 c.c. of wheat embryo extract resulted in

there was a considerable increase in weight. The addition of 3.5 and 7 gm. yeast, respectively, was followed by a weight increase of 370 gm. in eleven days. When yeast was omitted and starch (3 gm.) equivalent to the amount carried in the 7 gm. yeast was substituted, the weight became stationary, indicating that the gain was due to the antineuritic vitamin of the yeast rather than to the starch contained therein. A subsequent addition of yeast produced a slight gain in weight—50 grams in 5 days. At this time the low caloric value of the food—94 grams per kilogram, in all probability accounts for the small gain during the second yeast period.

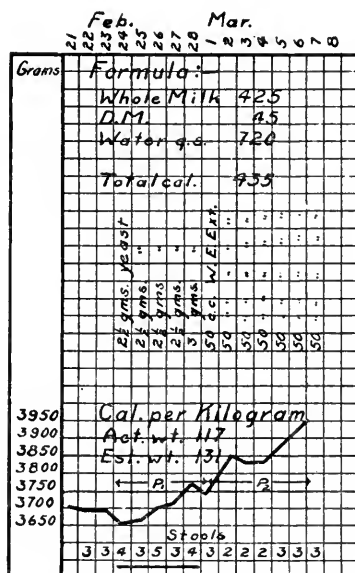


Fig. 6.—Leona L.; born January 8; birth weight, 3,040 gm.; age, 6 weeks.

At the time our other studies were being made there were in the hospital two rather severe cases of sudamina. Since Hawk¹² and his co-workers had obtained such good results with Baker's yeast in furunculosis, acne and other skin infections, it seemed desirable to test the effects of yeast on these two babies. In one case the infection had been running for about ten days, in the other case a somewhat shorter time. With both babies fairly large amounts of yeast—from 5 to 10 gm.—were used. During the period our staff were questioned each morning with regard to the condition of the babies. For a time several of them did not know that any treatment was being tried, so that their opinion

12. Hawk, P. B.; Knowles, F. C.; Rehfus, M. E., and Clarke, J. A.: J. A. M. A. **69**:1243, 1917.

was quite unbiased. There appeared to be no untoward results during the yeast additions, nor was there any apparent beneficial effects on the course of the infection. After days of yeast therapy the boils persisted. Indeed, in one other case (R.L.) boils developed during yeast feeding. The boils finally yielded in three days to the application of a dilute solution of iodine and benzol. In the cases noted there was no increase in weight, although fairly large amounts of yeast were used; nor was any diarrhea produced. The subsequent addition of 50 c.c. wheat embryo extract to the feedings was also without effect, indicating that stationary

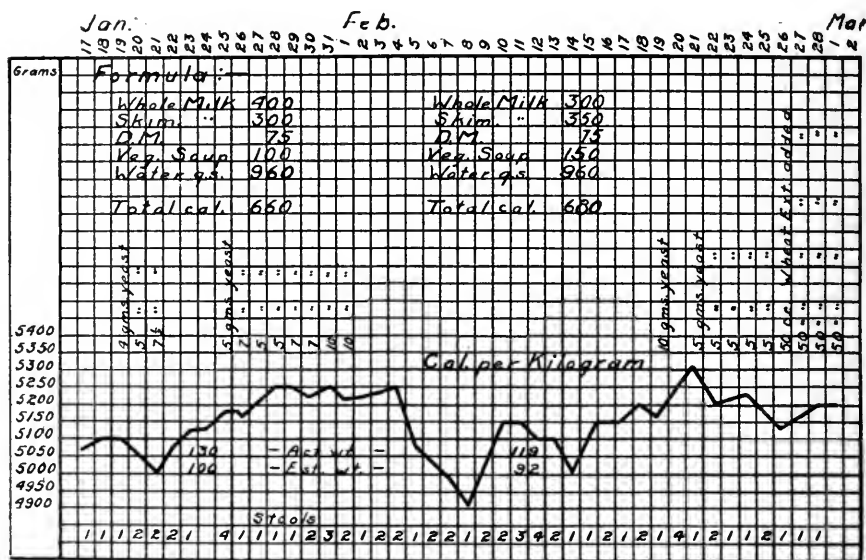


Fig. 7.—Robert G.; born July 10, 1920; birth weight, 3,247 gm.; age, 6 months.

weight in these cases was not due to a lack of the antineuritic vitamin. A failure to gain during an infection of this kind has been observed frequently.

Altogether, our experience with yeast points to the conclusion that it should not be used as a means of increasing the antineuritic content of infants' foods. All the babies under observation were well babies—that is, well from the standpoint of digestion. The addition of yeast, even in small amounts, resulted in diarrhea in a large number of cases, the untoward effects with the younger babies being more marked than with the older ones. Since in all probability the artificially fed baby most in need of some additional antineuritic vitamin will be the young baby, or the baby suffering from disturbed digestion, it is obvious that some substance other than yeast must be found as a means of supplying this.

A recent paper by Ladd¹³ on the effects of yeast in infant feeding, published since the above report was written, corroborates our findings in certain respects. The details of the investigation are not given, therefore, critical comparisons cannot be made. Ladd, however, was unable to obtain evidence that yeast had any therapeutic effect on the course of furunculosis in infants; nor was there any evidence in his studies that yeast in the amounts given influenced the rate of growth. In one case fermentative diarrhea developed soon after the yeast was begun.

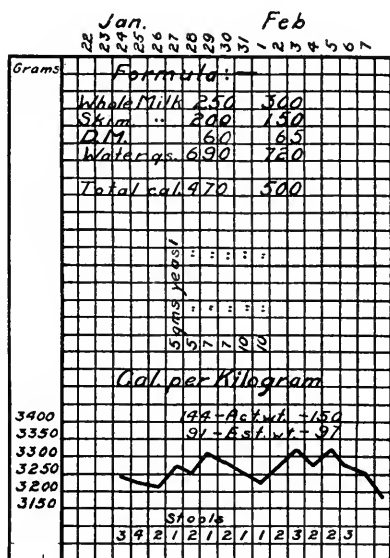


Fig. 8.—Wilbur Van H.; born Oct. 5, 1920; birth weight, 3,170 gm.; age, 3½ months.

REPORT OF CASES

CASE 1.—*Clarice P.* The stimulation of growth during Period 2 was apparently due to the yeast additions, since it followed a period of stationary weight. During the yeast period the stools became watery and more frequent. The substitution of 50 c.c. of wheat embryo extract (Period 3) resulted in a gain of 230 gm. in five days, against an increase of 150 gm. in the five day yeast period.

CASE 2.—*Robert L.* The addition of 5 and 7 gm. yeast, respectively, to the diet of Robert L., a baby who had always been a difficult feeding case, caused an increase in the number of stools and a subsequent loss in weight. Two and one-half grams were without effect on growth. The addition of 50 c.c. of wheat embryo extract resulted in an increase in weight.

CASE 3.—*Walter A.* Yeast produced no untoward results nor did it stimulate growth. Apparently, his failure to gain was due to some cause other than a lack of the antineuritic vitamin.

CASE 4.—*Julia McC.* The addition of 3 gm. yeast resulted in a temporary gain in weight. The increase in the number of diarrheal stools made it necessary to discontinue the yeast.

13. Ladd, M.: Arch. Pediat. **38**:423 (July) 1921.

CASE 5.—*Leona L.* The addition of 2.5 gm. yeast produced a slight gain in weight (Period 1). This, however, was accompanied by an increase in the number of stools. The substitution of 50 c.c. wheat embryo extract (Period 2) was more effective than the yeast. During this period the stools became normal.

CASE 6.—*Walter Van H.* was suffering from a severe case of sudamina. The addition of yeast in fairly large amounts—5, 7 and 10 gm., respectively—was without effect on growth; nor did the yeast appear to affect the course of the infection, which was subsequently cleared up after three days' treatment with a dilute solution of iodine and benzol.

CASE 7.—*Mary B.* The addition of 5 gm. yeast (dry weight) to the diet of this 7 weeks old baby produced diarrhea, manifested by many loose, watery stools.

CASE 8.—*Sybil T.* The addition of 5 gm. yeast produced severe diarrhea in a baby, 6 weeks old. Similar results were obtained three weeks later. At both times the effects were so marked that it was necessary to discontinue the yeast feedings.

CASE 9.—*Gretchen S.* The addition of yeast to the diet apparently stimulated growth without producing the untoward results observed in many of our other babies. This baby, however, was always quite constipated. The yeast additions were followed by soft yellow stools. During Period 3 the effect of 3.5 gm. of arrow starch (the amount contained in the yeast used) was tested. The weight remained stationary, indicating that the gain in Periods 2 and 4 were the results of the yeast additions. During Period 5 the caloric value of the food (94 calories per kilo on her theoretical weight) was too low to admit of gain in weight.

CASE 10.—*Keith M.* The addition of 2.5 and 3 gm., respectively, of dry yeast to the milk feedings produced no gain in weight. The effect on the stool was not marked. The substitution of 50 c.c. wheat embryo extract for the yeast resulted in a subsequent gain in weight.

CASE 11.—*Robert G.* The addition of yeast to the diet was without influence on growth. It also appeared to have no effect on a marked condition of sudamina. This baby apparently was not "well born" and had been a difficult feeding case from the first. The failure to grow was not caused by a lack of the antineuritic vitamin, as shown by the fact that the addition of 50 c.c. of our wheat embryo extract was also without effect.

THE INCIDENCE OF PROTEIN SENSITIZATION IN THE NORMAL CHILD *

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Although an extensive literature has accumulated on the diagnostic significance of protein sensitization tests in certain disease conditions, no attempt has hitherto been made to examine a large number of normal children for possible potential anaphylactic cases; nor have we been able to find any comparison between the incidence of protein sensitization in a large number of normal and abnormal subjects. The present widespread general interest in protein sensitization, first clinically and conclusively demonstrated by Schloss¹ and later by the voluminous and epochal researches of Walker,² suggested the necessity of this work.

It is the aim of this paper to show:

1. The incidence of protein sensitization in the normal child.
2. The relative frequency of sensitization to the specific protein in relationship to age and diet.
3. The relative frequency of sensitization to horse serum in those who have and those who have not been injected with prophylactic sera of any kind.

The children of this series were mostly Jewish, living on the East Side of Harlem and ranging in age from 2 to 15 years. The sexes were about evenly divided. A consideration of the diet of these children is necessary for a correct interpretation of the various protein reactions recorded. Of the cereal grains, wheat, corn, rice, rye, oats and barley are most common; it is interesting to note that the bread is practically without exception mostly rye. Eggs, milk and cheese are used freely. The meats most frequently eaten are beef and chicken, occasionally lamb and veal and not infrequently goose. Herring, smoked salmon, pike, smelts, and white fish are consumed often and in considerable quantities. Nearly all the different vegetables are used, especially potatoes and peas. As a rule, this class of children does not regularly indulge in vegetables and they are not encouraged to eat them. Fruits are eaten in season. Nuts are eaten occasionally. Milk, coffee and tea are indulged in freely.

Great care was exercised in the selection of the children to be tested. Each child's history was inquired into carefully and a thorough

* Received for publication, Sept. 15, 1921.

¹ From the Children's Clinic, Mount Sinai Hospital, New York.

1. Schloss, O. M.: *Am. J. Dis. Child.* **3**:341 (April) 1912.

2. Walker, I. C., and Adkinson, J.: *J. M. Research* **32**:287, 1917.

physical examination made. Only those presenting negative histories and physical evidence of a possible or probable anaphylaxis were tested. The children considered anaphylactic in origin were as follows: Bronchial asthma, recurrent bronchitis, seasonal and perennial hay fever, periodic vomiting, gastro-enteritis, acute and chronic eczema, urticaria, dermatoses, erythema multiforme, angioneurotic edema, iritis and conjunctivitis.

Selection of Protein.—It is extremely important to select the proper material, especially in a series of this character. The protein must be readily soluble and contain all the proteins composing the food.³ The activity of most of the proteins was assured by definitely positive reactions in known anaphylactic cases. The protein dilutions were prepared fresh every five days and kept in well corked vials in the icebox. For use the protein was dissolved in tenth normal sodium hydroxid in a strength of 1:50.

Technic of the Tests.—The cutaneous scratch test is the one solely employed. After the flexor surface of the forearm has been cleaned with alcohol, linear cuts about $\frac{1}{8}$ inch long and $1\frac{1}{2}$ inches apart are made with a sharp scalpel. The cuts should be deep enough to penetrate the outer layers, without drawing blood. While blood does not interfere with the test, we consider it poor technic and unnecessary. Enough cuts are made at one time for all the proteins to be tested, allowing two for controls. The location of these controls is important; one is near the bend of the elbow where the skin is more sensitive, the second control is placed near the wrist, the tests are made between these two points. On each cut is placed a drop of the test solution. One drop of the tenth normal sodium hydroxid is placed on the controls. After the dissolved protein has remained in contact with the cuts for one half hour, it is wiped away and the reading made. The reactions are always to be compared with the controls. During the test, the proteins must be kept in solution and drying prevented by the addition of a drop tenth normal sodium hydroxid.

If a reaction appears within a few minutes and rapidly becomes larger accompanied by an intense erythema and itching, it is well to wipe away the protein and thus prevent further absorption and the disagreeable symptoms of a possible acute anaphylaxis. It must be remembered that even cutaneous tests are not without danger of inducing anaphylactic shock.

Skin Irritability.—If the skin of a patient shows evidence of irritability, this fact should be noted for the proper final interpretation. The less the skin is traumatized, the less the danger of irritation. The

3. All proteins we used were prepared by the methods and under the supervision of R. P. Wodehouse.

manifestations may be in the form of wheals of different sizes, varying degrees of erythema, or both. These pseudoreactions may appear almost immediately after the cuts are made and be present at the time the true reactions are read. At times cutaneous irritability disappears within from five to ten minutes after the cuts are made, thus not interfering with a proper final reading. At other times it does not begin to appear until from fifteen to twenty minutes after the tests are made. The controls in such cases are very important guides. It is best to make a single row of tests down the forearm about two inches apart and if the tests are repeated, little or no irritability is encountered, enabling us to interpret the end-results more easily and with greater certainty.

Types of Reaction.—Due to a lack of standardization of technic and classification of the reactions, much of the statistical data presented in the literature is more or less confusing, which tends to distract from its value. The technic in our series was carried out by one of us (M. M. P.) thus assuring uniformity of procedure.

The classification we adopted is essentially the one employed by Walker² and is briefly as follows:

1. Positive reaction: (a) Distinct urticarial wheal, 0.5 cm. or more in diameter, surrounded by a zone of erythema in the presence of a negative control. The wheal is always irregular in outline, caused by edema spreading along the lymph spaces.

- (b) Distinct urticarial wheal, less than 0.5 cm. in diameter, surrounded by a zone of erythema of two or more cm.

- (c) Only a zone of erythema of two or more cm., with little or no elevation about the cut.

2. Doubtful reaction: All reactions measuring less than the above and more than the control.

3. Delayed reaction: This reaction is described by Walker as negative at the end of one half hour, but on the following day the cut appears like a slight infection; the surrounding skin is hot, very red and slightly elevated. Frequently the cut contains pus which is always sterile. This reaction was not noted in our series as the patients were not observed for the twenty-four hours following the tests.

4. Negative reaction: Those not differing in any way from the control.

The Cutaneous Versus the Intracutaneous Reaction.—We have adopted the cutaneous in preference to the intracutaneous test only after very careful and diligent comparisons. The same conclusion was reached by Schloss⁴ who said:

4. Schloss, O. M.: Am. J. Dis. Child. **19**:433 (June) 1920.

During the past few years I have used the cutaneous test entirely as opposed to the intracutaneous test. This was done only after having made a series of tests by both methods on normal patients and on patients suffering from definite food idiosyncrasy. Such tests were made on 100 infants and children not apparently suffering from disturbances due to food, and in thirty who suffered from definite symptoms due to the ingestion of some variety of food. . . . The intracutaneous test is more sensitive. In three patients later proved to have mild idiosyncrasy to milk, intracutaneous tests proved positive while cutaneous tests were negative. This seems to be the only point in favor of the intracutaneous test.

Against it is the fact that it is apt to be misleading. Pseudoreactions occur which are difficult to interpret and in some instances patients give reactions which seem positive despite the lack of clinical evidence that the substance tested causes any symptoms. Many vegetable proteins are difficult to obtain in a form soluble in physiologic sodium chlorid solution, but are soluble only in alkaline solvents. Such solutions cannot be used for intradermal tests. To insure sterility, the proteins must be prepared carefully, which adds considerable technical difficulty. On two occasions I have seen severe infections due to such tests. Another objection is that a very sensitive patient may be made seriously ill by the injection of even a minute amount of the protein to which he reacts. In consideration of these objections it seems that, for general use the cutaneous test is the one to be chosen.

Walker² also concludes that:

The skin test is specific; it separates closely related proteins; it is sufficiently sensitive and yet not too sensitive; . . . it is easy to do, and it does not inconvenience the patient. The intradermal test is much less specific; it does not always separate closely related proteins, therefore it may be non-specific; it is much too sensitive, therefore it is . . . very erratic; it is also more difficult to do, and it causes the patient considerable annoyance and discomfort. Therefore, it is not as practical when many proteins must be tested.

The Cutaneous Reaction in the Normal Child.—Formerly, when a patient with a positive or doubtful reaction developed symptoms resembling any of the now familiar anaphylactic states and the reaction was proved not to be the etiologic factor in the production of the symptoms, the phenomenon was considered an accidental protein sensitization of no significance. It is our belief that, when such reactions occur, these patients are fertile soil and always in danger of developing an anaphylactic condition. We maintain that a normal child exhibiting a skin reaction above the control is a potential anaphylactic case and should be regarded as such.

It must be borne in mind that these children are free from all anaphylactic symptoms because they have acquired a certain amount of individual tolerance against the specific protein causing sensitization. Symptoms develop only when the intake of that protein surpasses the threshold of tolerance. The limit of tolerance varies in different individuals as well as in the same individual at different times. Consequently, it is impossible to predetermine one's tolerance to proteins, or foretell the onset of anaphylactic symptoms by the degree of the skin reaction. A positive reaction does not necessarily predicate the onset of symp-

toms in one case while a doubtful reaction may augur a very violent attack. Two cases in point are the following:

History.—C. H., male, 5½ years of age, white, one of a family of eight, one of our series, was last tested in May, 1921. Fifty-two proteins were tested, of which the following showed sensitization: Horse dander, dog hair, cat hair and fig gave positive reactions; egg whole, egg white, cucumber, asparagus, sweet potato, buckwheat, chestnut, chicken feathers and tea gave plus minus reactions. Aug. 16, 1921, he returned to the clinic suffering from a typical attack of bronchial asthma; symptoms much worse at night.

Treatment.—The treatment instituted was a corrective diet, and when he returned two weeks later, he was free from his asthma and as well as ever.

History.—J. T., male, aged 14, white, not in our normal series, has been having attacks of bronchial asthma for the past four years. He was tested against seventy-three proteins consisting of food, serum, epidermal and bacterial. He gave a positive reaction to rabbit hair and a plus minus reaction to horse serum and lamb. These tests were repeated a number of times.

Sept. 16, 1921, he was given a prophylactic dose of 1 c.c. (1,000 units) diphtheria antitoxin⁵ and within fifteen minutes he was seized with a severe attack of dyspnea lasting an hour, marked respiratory oppression and profuse expectoration; one-half hour later there developed a generalized erythema and giant urticaria with severe itching, edema of the hands, lips, cheeks and eyelids, marked vertigo, vomiting and cramps. September 17 he was entirely free from asthma, the rash had disappeared, but swellings still were present. He was tested with horse dander and horse serum which gave very distinct reactions. The reaction to rabbit hair was more intense than ever before. September 19 rabbit hair only gave a positive reaction; horse dander and serum, horse dander alkali metaprotein and horse dander peptone gave negative reactions.

Much of the sensitization occurring in children takes place through the intestinal tract. Talbot⁶ found that "during infancy and childhood practically all cases of sensitization are due to foods." Because of adaptation or desensitization, allergy to food becomes less common as the age of puberty is reached. The author cites literature to show that the gastro-intestinal tract of the newly born infant is permeable to undigested foreign proteins, hence the infant develops the power of destroying such protein up to its limit of tolerance.

In 1913, Richet⁷ stated that "experimental alimentary anaphylaxis is difficult to bring about under conditions of healthy digestion . . . because the individual passes a minimal quantity of unchanged albumin."

Vaughn⁸ asserts that the sensitized group resulting from protein digestion is destroyed in normal digestion; that it is only under abnormal conditions that protein sensitization results through the alimentary tract.

Schloss and Worthen⁹ found that the intestinal tract of normal infants is usually impermeable to undigested foreign protein. In

5. Health Department, New York City.

6. Talbot, F. B.: Boston M. & S. J. **175**:409, 1916; **179**:385, 1918.

7. Richet, C.: Seventeenth Internat. Cong. Med., Lond., 1913, Sect. 4, Pt. 1, p. 13.

8. Vaughn: Protein Split Products, 1913.

9. Schloss, O. M., and Worthen, T. W.: Am. J. Dis. Child. **11**:342 (April) 1916.

agreement with other observers quoted by them, they also found that in nutritional or gastro-enteric disorders, foreign protein may be absorbed in an undigested or partially digested state and appear in the urine.

Thus comparing these findings with the evidence presented in Tables 1 to 15, one can understand how sensitization can readily occur in normal children who occasionally have some gastro-enteric disorder, and who acquire sufficient tolerance to their particular dietary to ward off symptoms of the anaphylactic state.

When that tolerance is exceeded, anaphylactic symptoms become evident. A positive reaction in the normal child may not have the same significance as a doubtful reaction in the abnormal child even though he shows multiple positive reactions.

C. T., a white male child, aged 10, suffering from repeated attacks of bronchial asthma for the past eight years (referred by Dr. Mary Rose) gave positive reactions to buckwheat, wheat glutenin, and globulin, potato, cattle hair and horse serum and doubtful reactions to oats, corn, rice, rye, lima beans, beans and horse dander. After careful study he was permitted to have all food except oatmeal, improvement followed immediately and was very evident two days after change in diet. This case distinctly shows tolerance for the positive-reacting proteins and not the doubtful reacting proteins.

Caulfield¹⁰ has presented cases which show that it is possible for one to escape the clinical manifestations of anaphylaxis even though sensitized to proteins to which exposure is inevitable.

TABLE 1.—CASES TESTED FOR SENSITIZATION TO CEREAL GRAINS

Protein	Number Tested				Percentage		
	2-5 Years	5-10 Years	10-15 Years	Total	Posi- tive	Doubt- ful	Nega- tive
Wheat.....	24	100	76	200	0	2	98
Corn.....	24	100	76	200	0	0.5	99.5
Rice.....	24	100	76	200	0	0.5	99.5
Rye.....	24	100	76	200	0.5	8.5	91
Oats.....	24	100	76	200	0	1	99
Barley.....	24	100	76	200	0	1.5	98.5
Buckwheat.....	11	63	30	104	0	1.92	98.08

Considering the data presented in the present series, Tables 1 to 8 show the results of the various food proteins tested. In Table 1 the total number of doubtful reactions was thirty among twenty-six children, equally divided as to sex. The one positive reaction to rye occurred in a boy aged 12 years. It is interesting to note seventeen doubtful reactions to rye.

10. Caulfield, A. W.: J. A. M. A. 76:1071 (April 16) 1921.

The total number of doubtful reactions to egg and milk (Table 2) were eleven occurring in six cases. There were no positive reactions.

TABLE 2.—CASES TESTED FOR SENSITIZATION TO EGGS AND MILK

Protein	Number Tested				Percentage		
	2-5 Years	5-10 Years	10-15 Years	Total	Posi- tive	Doubt- ful	Nega- tive
Egg, whole.....	19	111	74	204	0	1.96	98.04
Egg white.....	19	111	74	204	0	1.96	98.04
Egg yolk.....	19	111	74	204	0	0.98	99.02
Milk, cow's.....	19	111	74	204	0	0	100
Casein.....	19	111	74	204	0	0	100
Lactalbumin.....	19	111	74	204	0	0	100
Cheese.....	12	55	38	105	0	0.94	99.16

When the meat tests were conducted turkey and pork were used as controls, since they are rarely ingested by these children. Four cases showed doubtful reactions, equally divided between beef and veal (Table 3).

TABLE 3.—CASES TESTED FOR SENSITIZATION TO MEATS

Protein	Number Tested				Percentage		
	2-5 Years	5-10 Years	10-15 Years	Total	Posi- tive	Doubt- ful	Nega- tive
Beef.....	13	61	30	104	0	1.94	98.06
Chicken.....	13	61	30	104	0	0	100
Lamb.....	13	61	30	104	0	0	100
Veal.....	13	61	30	104	0	1.94	98.06
Goose.....	13	61	30	104	0	0	100
Turkey.....	13	61	30	104	0	0	100
Pork.....	13	61	30	104	0	0	100

Only one child shows a doubtful reaction to fish (Table 4); the control protein in this series was taken from the oyster.

TABLE 4.—CASES TESTED FOR SENSITIZATION TO FISH

Protein	Number Tested				Percentage		
	2-5 Years	5-10 Years	10-15 Years	Total	Posi- tive	Doubt- ful	Nega- tive
Herring.....	12	55	38	105	0	0	100
Salmon.....	12	55	38	105	0	0	100
Pike.....	12	55	38	105	0	0	100
Smelts.....	12	55	38	105	0	0.94	99.06
Mackerel.....	12	55	38	105	0	0	100
Bluefish.....	12	55	38	105	0	0	100
Haddock.....	12	55	38	105	0	0	100
Oyster.....	12	55	38	105	0	0	100

Of nineteen vegetables tested only six gave a doubtful reaction (Table 5). These were asparagus, cucumber, lettuce, peas, white potato and sweet potato; four children showed the reaction.

TABLE 5.—CASES TESTED FOR SENSITIZATION TO VEGETABLES

Protein	Number Tested				Percentage		
	2-5 Years	5-10 Years	10-15 Years	Total	Posi- tive	Doubt- ful	Nega- tive
Beans.....	11	52	41	104	0	0	100
Asparagus.....	11	63	30	104	0	0.96	99.04
Beet.....	10	56	40	106	0	0	100
Cabbage.....	11	52	41	104	0	0	100
Carrot.....	8	60	37	105	0	0	100
Cauliflower.....	14	61	32	107	0	0	100
Cucumber.....	14	61	32	107	0	0.93	99.07
Celery.....	10	56	40	106	0	0	100
Lentil.....	10	56	40	106	0	0	100
Lettuce.....	10	56	40	106	0	0.94	99.06
Linna bean.....	14	61	32	107	0	0	100
Onion.....	10	56	40	106	0	0	100
Peas.....	11	52	41	104	0	0.96	99.04
Potato.....	11	52	41	104	0	0.96	99.04
Radish.....	14	61	32	107	0	0	100
Rhubarb.....	10	56	40	106	0	0	100
Spinach.....	10	56	40	106	0	0	100
Sweet potato.....	14	61	32	107	0	0.93	99.07
Tomato.....	10	56	40	106	0	0	100

When fruits were tested, one boy gave a positive reaction to plum, four others gave a doubtful reaction to fig (Table 6).

TABLE 6.—CASES TESTED FOR SENSITIZATION TO FRUITS

Protein	Number Tested				Percentage		
	2-5 Years	5-10 Years	10-15 Years	Total	Posi- tive	Doubt- ful	Nega- tive
Orange.....	8	60	37	105	0	0	100
Banana.....	8	60	37	105	0	0	100
Grape fruit.....	8	60	37	105	0	0	100
Strawberry.....	8	60	37	105	0	0	100
Peach.....	8	60	37	105	0	0	100
Pear.....	8	60	37	105	0	0	100
Pineapple.....	8	60	37	105	0	0	100
Cantaloupe.....	8	60	37	105	0	0	100
Fig.....	14	61	32	107	0	3.73	96.27
Plum.....	14	61	32	107	0.93	0	99.07
Raspberry.....	14	61	32	107	0	0	100
Blackberry.....	14	61	32	107	0	0	100

Only one child gave a doubtful reaction to nuts (Table 7). This sensitiveness was shown to chestnut.

TABLE 7.—CASES TESTED FOR SENSITIZATION FOR NUTS

Protein	Number Tested				Percentage		
	2-5 Years	5-10 Years	10-15 Years	Total	Posi- tive	Doubt- ful	Nega- tive
Almonds.....	11	52	41	104	0	0	100
English walnut.....	11	52	41	104	0	0	100
Peanut.....	11	52	41	104	0	0	100
Brazil nut.....	11	52	41	104	0	0	100
Chestnut.....	11	63	30	104	0	0.96	99.04

The common beverages, coffee, tea and cocoa, gave three doubtful reactions; two for coffee and one for tea; one child was sensitive to both (Table 8).

TABLE 8.—CASES TESTED FOR SENSITIZATION TO BEVERAGES

Protein	Number Tested				Percentage		
	2-5 Years	5-10 Years	10-15 Years	Total	Posi- tive	Doubt- ful	Nega- tive
Coffee.....	11	63	30	104	0	1.92	98.08
Tea.....	11	63	30	104	0	0.96	99.04
Cocoa.....	11	63	30	104	0	0	100

In Table 9 are presented the results of tests with the proteins from the epidermis of the horse, dog, cat, chicken and goose. The three positive reactions occurred in a boy aged 5½ years. Six doubtful reactions were observed in six children. The children who showed doubtful reactions to horse dander gave negative reactions to horse serum and had never received injections of any kind of serum.

TABLE 9.—CASES TESTED FOR SENSITIZATION TO EPIDERMAL PROTEINS

Protein	Number Tested				Percentage		
	2-5 Years	5-10 Years	10-15 Years	Total	Posi- tive	Doubt- ful	Nega- tive
Horse dander.....	19	111	74	204	0.49	1.96	97.55
Dog hair.....	11	63	30	104	0.96	0.96	98.08
Cat hair.....	11	63	30	104	0.96	0	99.04
Chicken feathers.....	11	63	30	104	0	0.96	99.04
Goose feathers.....	11	63	30	104	0	0	100

The incidence of sensitization to horse serum was determined by a more extensive series of tests to determine the relative safety of administering diphtheria antitoxin. The only child who gave a doubtful reaction to horse serum (Table 10) was a boy, aged 3½ years, whose history as to diphtheria was negative and who had never received an injection of any kind of serum.

TABLE 10.—CASES TESTED FOR SENSITIZATION FOR HORSE SERUM

Age	Number Cases	Number Positive	Number Doubtful	Number Negative
2.....	3	0	0	3
3.....	27	0	1	26
4.....	26	0	0	26
5.....	50	0	0	50
6.....	50	0	0	50
7.....	54	0	0	54
8.....	56	0	0	56
9.....	44	0	0	44
10.....	51	0	0	51
11.....	50	0	0	50
12.....	30	0	0	30
13.....	27	0	0	27
14.....	9	0	0	9
Total.....	477	0	1	476

Table 11 shows the interval between the injection of diphtheria antitoxin and the skin test for horse serum. Eighty children were tested and all reacted negatively. Four were injected twice as they had the disease twice.

TABLE 11.—INTERVAL BETWEEN HORSE SERUM (DIPHTHERIA ANTITOXIN) INJECTION AND DATE WHEN HORSE SERUM TESTS WERE MADE

Interval	No. Cases	Interval	No. Cases
1-6 months.....	2	6½ years.....	2
6 months.....	3	7 years.....	3
1 year.....	9	7½ years.....	1
1½ years.....	4	8 years.....	5
2 years.....	5	8½ years.....	3
2½ years.....	6	9 years.....	2
3 years.....	10	9½ years.....	1
3½ years.....	1	10 years.....	1
4 years.....	3	10½ years.....	1
4½ years.....	4	11 years.....	2
5 years.....	8	11½ years.....	2
5½ years.....	5	12 years.....	1
6 years.....	6		
Total.....			84

Table 12 gives the ages of the patients at the time of testing.

TABLE 12.—AGE OF PATIENTS AT TIME OF TESTING FOR HORSE SERUM AND HAVING HAD INJECTIONS OF DIPHTHERIA ANTITOXIN

Age, Years	No. Cases	Age, Years	No. Cases
2.....	0	9.....	10
3.....	0	10.....	8
4.....	4	11.....	6
5.....	3	12.....	8
6.....	7	13.....	4
7.....	12	14.....	5
8.....	13		
Total.....			80

All positive reactions of the entire series are summarized in Table 13. There was none among the children aged from 2 to 5 years. Two boys in the five to ten year period gave four positive reactions; one boy in the from ten to fifteen year period was sensitive to rye. Thus in a series of 719 tests, there were five children who gave positive reactions. These occurred in three boys. The boy who was sensitive to horse dander, dog hair and cat hair gave a negative history and reaction to horse serum injection.

TABLE 13.—SUMMARY OF THE POSITIVE REACTIONS

Protein	2-5 Years		5-10 Years		10-15 Years		Total Number Tested	Number Positive
	Number Tested	Number Positive	Number Tested	Number Positive	Number Tested	Number Positive		
Rye.....	24	0	100	0	76	1	200	1
Plum.....	14	0	61	1	32	0	107	1
Horse dander.....	19	0	111	1	74	0	204	1
Dog hair.....	11	0	63	1	30	0	104	1
Cat hair.....	11	0	63	1	30	0	104	1
Total.....	79	0	398	4	242	1	719	5

In Table 14 we have a summary of the total number of doubtful reactions, sixty-seven in a series of 4,274 tests.

TABLE 14.—SUMMARY OF THE DOUBTFUL REACTIONS

Protein	2-5 Years		5-10 Years		10-15 Years		Total Number Tested	Number Doubtful	
	Number Tested	Number Doubtful	Number Tested	Number Doubtful	Number Tested	Number Doubtful			
Wheat.....	24	1	100	2	76	1	200	4	
Corn.....	24	1	100	0	76	0	200	1	
Rice.....	24	0	100	0	76	1	200	1	
Rye.....	24	6	100	10	76	1	200	17	
Oat.....	24	0	100	2	76	0	200	2	
Barley.....	24	1	100	2	76	0	200	3	
Buckwheat.....	11	0	63	2	30	0	104	2	
Egg, whole.....	19	0	111	3	74	1	204	4	
Egg white.....	19	0	111	3	74	1	204	4	
Egg yolk.....	19	0	111	2	74	0	204	2	
Cheese.....	12	0	55	0	38	1	105	1	
Beef.....	13	0	61	2	30	0	104	2	
Veal.....	13	1	61	1	30	0	104	2	
Smelts.....	12	0	55	1	38	0	105	1	
Asparagus.....	11	0	63	1	30	0	104	1	
Cucumber.....	14	0	61	1	32	0	107	1	
Lettuce.....	10	0	56	1	40	0	106	1	
Peas.....	11	0	52	0	41	1	104	1	
Potato.....	11	0	52	1	41	0	104	1	
Sweet potato.....	14	0	61	1	32	0	107	1	
Fig.....	14	0	61	3	32	1	107	4	
Coffee.....	11	1	63	0	30	0	104	1	
Tea.....	11	1	63	1	30	0	104	2	
Chestnut.....	11	0	63	1	30	0	104	1	
Horse dander.....	19	1	111	0	74	3	204	4	
Horse serum.....	56	1	254	0	167	0	477	1	
Dog hair.....	11	0	63	1	30	0	104	1	
Chicken feather.....	11	0	63	1	30	0	104	1	
Total.....	477	14	2,314	42	1,483	11	4,274	67	
							M	F	
(2- 5 years) Total number \pm reactions were 14 distributed among 9 patients								6	3
(5-10 years) Total number \pm reactions were 42 distributed among 30 patients								18	12
(10-15 years) Total number \pm reactions were 11 distributed among 9 patients								5	4
(2-15 years) Total number \pm reactions were 67 distributed among 48 patients								29	19

The total number of children tested was 502. The total number of tests performed was 9,406. Seventy-four different proteins were used in these tests, averaging 18.73 proteins per case. It is interesting to note that rye (bread commonly eaten by these children) gave 3.38 per cent. doubtful reactions of the total actual number of cases tested.

The summary of the entire series is presented in Table 15.

TABLE 15.—SUMMARY OF REACTIONS IN RELATION TO ACTUAL NUMBER OF CASES TESTED AND TESTS PERFORMED

Age, Years	Actual Number of Cases Tested	Number of Tests Performed	Number of Positive Reactions	Per Cent. Cases With Positive Reactions	Per Cent. Positive Reactions to No. of Tests Performed	Number of Doubtful Reactions	Per Cent. of Cases With Doubtful Reactions	Per Cent. Doubtful Reactions to No. of Tests Performed	Cases With Positive Reactions	Cases With Doubtful Reactions
2-5	58	1,008	0	0	0	14	15.5	1.38	0	9
5-10	270	5,136	4	0.70	0.07	42	11.11	0.81	2	30
10-15	174	3,262	1	0.57	0.03	11	5.17	0.33	1	9
Total	502	9,406	5	0.53	0.05	67	9.56	0.71	3	48

CONCLUSIONS

1. Ten per cent. of the children show doubtful and positive reactions which decrease as their age increases, indicating progressive desensitization. This coincides with Talbot's observations.

2. The incidence of sensitization in normal as compared with abnormal children indicates that the ratios are correct. To compare our incidence of sensitization with a pathologic series, we have found the report of Walker¹¹ the most complete. The author tabulates 400 cases of bronchial asthma and makes the following statements; four-fifths of the patients whose asthma began during infancy were sensitive; two-thirds of those whose asthma began during childhood were sensitive; one-half of those whose asthma began during young adult life were sensitive; one-fourth whose asthma began during adult life were sensitive, none were sensitive who began after middle life.

3. The foods giving doubtful and positive reactions are those frequently indulged in and compose an essential part of the dietary of these children.

4. The foods giving the greatest number of reactions in these normal children correspond proportionately with those in the abnormal children.

5. The administration of diphtheria antitoxin incurs practically no risk of anaphylaxis.

6. All reactions above the control are true protein sensitizations and should be regarded as potential anaphylactic cases.

7. It is necessary to institute prophylactic measures in normal cases presenting sensitization without symptoms.

11. Walker, I. C.: A Clinical Study of 400 Patients with Bronchial Asthma, *Canad. M. Assn. J.* 9:97 (Feb.) 1919.

AN UNUSUAL EXANTHEM OCCURRING IN INFANTS*

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During the past year I have observed several cases of an unusual nature occurring in infants. These cases were characterized by an acute illness, with high fever, lasting from three to four days. The temperature then fell quickly to normal, and with the subsidence of the fever an eruption appeared lasting from one to three days. The patients were all infants whose ages ranged from 9 months to 2 years. Only one member of a family contracted the disease. The following protocol of the first case observed during March, 1921, will serve as an example of this condition.

REPORT OF CASE

History.—Baby H. T., aged 9 months, became suddenly ill March 10, 1921. He had been perfectly well the day before and had not been out of the house for at least two weeks prior to his illness.

Physical Examination.—Examination showed a well nourished and developed infant, acutely ill and extremely irritable. There was no toxemia. The head was normal in shape and size and the anterior fontanel was level. There was no discharge from the nose. The ear drums were normal. The throat was slightly congested. The tongue was normal. No Koplik's spots were seen on the mucous membranes. There was no adenitis. The examination of the heart and lungs was negative, likewise the examination of the abdomen. The reflexes were normal. No eruption was seen on the skin. The temperature was 104 F.; pulse, 160; respirations, 35.

Laboratory Examination.—Urine was negative for albumin, sugar, casts and leukocytes. The white blood count was 5,400, with 85 per cent. lymphocytes and 15 per cent. polymorphonuclears.

The temperature remained between 103 and 104 F. for three days. During this time the patient was seen daily and examined carefully. No cause for the temperature was found. The infant seemed quite ill, but not toxic. Most of his feedings were refused.

Exanthem.—March 13, the fourth day of the disease, a telephone message was received from the mother stating that the baby's fever was down and he was much better, but that he had an eruption which she thought resembled measles. The temperature was 98 F. The baby was much less irritable and was taking his feedings well. No Koplik's spots were observed. The skin was covered with a discrete maculopapular eruption most marked on the trunk. However, there were some lesions on the face and extremities. The lesions were rose red in color and varied in size from a pin head to a large pea. There was no pruritis. The mother noticed that the eruption had first appeared on the neck and had quickly spread downward. The following day the eruption began to fade. The baby's condition was excellent. Two days later the eruption had completely disappeared. There was a very faint desquamation. A brother, aged 4, who was directly exposed to the baby throughout the illness did not contract the disease.

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* From the Department of Pediatrics and Infectious Diseases, University of Michigan Medical School, Dr. D. M. Cowie, Director.

Seven other cases were observed during the next four months. They all followed the same course, a period of fever for three or four days with a sudden drop in temperature coincident with an eruption lasting from two to three days and then disappearing. The first case was regarded as a toxic eruption of unknown origin. As more cases were observed it became evident that this was a definite disease entity which followed a course similar to the acute exanthemata of infancy and childhood.

Veeder and Hempleman¹ recently reported a series of cases of a similar nature. They believe that they are describing the same condition that was described by Zahorsky² in 1910. My series of cases corresponds almost exactly with those of Veeder and Hempleman and Zahorsky.

Age.—The disease occurred in patients whose ages ranged from 9 months to 2 years. None of the infants were breast fed. Veeder and Hempleman have observed this condition in older children, but state that it has a predilection for infants.

Symptoms.—In all cases the illness occurred suddenly, the patients being perfectly well the day before. At the onset the prominent symptoms were fever, irritability, and refusal of food. The fever during the pre-eruptive period ranged from 102 to 105 F. The drop in temperature and the appearance of the eruption were always coincident with a lessening of irritability and a return of the appetite. The extensive eruption apparently caused no symptoms. In spite of the high fever the infants were not toxic.

Physical Signs.—These were conspicuous by their absence. No cause for the temperature could be found before the eruption appeared. Careful routine examination including the ears was always negative.

Eruption.—The lesions were mostly macules, but papules were also present. They were about one-eighth of an inch in diameter and pale or rose red in color. They could be pressed out easily and no hemorrhagic lesions were ever seen. The eruption had the general blotchy appearance of a measles eruption, but no crescentic arrangement was ever seen. The eruption usually was noticed first on the neck and quickly spread downward. It was more pronounced on the neck and trunk than on the face and extremities. The entire course of the eruption was from two to three days. There was a very faint desquamation.

1. Veeder and Hempleman: A Febrile Exanthem Occurring in Childhood, Tr. Am. Ped. Soc., June, 1921; abstr. J. A. M. A. **77**:312, 1921.

2. Zahorsky: Roseola Infantum, Pediatrics, **22**:60 (July 23) 1910.

Through the courtesy of Drs. Veeder and Hempleman, I was able to obtain a copy of their paper before publication and also to obtain the reference to Zahorsky's article.

Laboratory Findings.—The urine was examined in all cases and was found to be uniformly negative. Veeder and Hempleman call particular attention to the blood picture which is characterized by a leukopenia and a high lymphocytosis. In three of my cases in which a blood count was done, exactly the same picture was found. The lymphocytosis in the three cases was always over 80 per cent. This seems to be an important point.

Contagion.—The disease occurred in only one member of each family. It did not seem to be contagious.

Diagnosis.—When the temperature drops and the eruption appears, the diagnosis is very easy. During the pre-eruptive period one thinks of pyelitis, otitis media and pneumonia. The blood count and differential picture is very helpful at this stage. The eruption resembles measles more than anything else. However, measles is easily excluded by the absence of Koplik's spots and by the fact that as the eruption appears, the temperature drops and the patient seems perfectly well.

Rubella is also to be considered. In rubella there is usually no prodromal period of fever before the eruption such as was observed in these cases. In rubella the fever is much lower than is observed here. Also there is no post-auricular adenitis as is usually seen in rubella.

The only exanthem which has a stormy pre-eruptive period, followed by well being when the eruption appears, is variola. However, the condition has nothing in common with variola. There also remains to be considered toxic or anaphylactic eruptions caused by various proteins, food and bacterial. No definite evidence of this etiology could be demonstrated. None of the patients were taking any drugs before their illness.

Treatment.—The treatment is purely symptomatic. The eruption disappears spontaneously. There have been no complications.

DISCUSSION

It is my belief that this is a definite disease entity, not described in any of the present day pediatric textbooks. Veeder and Hempleman have proposed the name "Exanthem Subitum" to describe this condition as the most characteristic thing is the sudden appearance of the eruption on the fourth day.

CONCLUSIONS

An unusual disease occurring in infants is described. It is characterized by a pre-eruptive period of three to four days with high fever. On the fourth day there is a sudden drop in temperature coincident with an eruption. The eruption last one to two days and is maculopapular resembling measles. The etiology is unknown.

THE RESPIRATORY EXCHANGE IN A CASE OF BILIARY ATRESIA *

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The study of the respiratory exchange in a case of biliary atresia was undertaken to see whether the presence of large quantities of unabsorbed fat in the intestine had any influence on the absorption of carbohydrate. It is held by many that fat is the *fons et origo mali* of many cases of marasmus and malnutrition in infancy. It has been shown that in these conditions fat can be absorbed from the intestine¹ and metabolized in the tissues,² but it has not been shown whether the presence of fat in the intestine is any impediment to the absorption of other forms of food. This case of biliary atresia seemed to afford an opportunity of seeing whether large quantities of unabsorbed fat in the intestine inhibited the absorption of carbohydrate.

REPORT OF CASE

History.—J. S., female, aged 8 weeks, was admitted to the Royal Hospital for Sick Children, Glasgow, Jan. 10, 1921, with a history of jaundice of two weeks' duration. She was a first child and the parents were healthy. Labor occurred at full term; it was normal and the child seemed to be healthy at birth. It thrived well at first. At the age of 6 weeks jaundice was first noticed, and this gradually increased in intensity. The stools which at first were pigmented are said gradually to have become paler and paler. Otherwise the child seemed healthy and was increasing in weight.

Physical Examination.—On admission the child appeared to be fairly well nourished, weight 7 pounds 9 ounces, but deeply jaundiced. The examination of the heart and lungs was negative. The liver was palpable two finger breadths below the costal margin. The spleen was not palpable. The stools were clay colored and did not contain hydrobilirubin. The urine contained much bile pigment. The von Pirquet and Wassermann reactions were negative. From January till April 27 the child progressed slowly. The weight increased to 9 pounds 10 ounces, but the jaundice gradually increased in intensity. On April 27, the temperature rose. An ulcerative pharyngitis developed. The blood culture gave a pure growth of streptococci. The child died, May 4.

Necropsy Report.—At the postmortem examination no traces of the gall-bladder or bile ducts could be found, their position being occupied by strands of fibrous tissue without any evidence of a lumen. The liver showed a generalized cirrhosis of the biliary type. The pancreatic ducts opened normally in the papilla of Vater. Otherwise, the findings were those of a general septicemia.

* Received for publication, Aug. 25, 1921.

* From the Royal Hospital for Sick Children.

* The expenses of this investigation were defrayed by the Medical Research Council.

1. Hutchison: Quart. J. M. **13**:277 (April) 1920.

2. Fleming: Quart. J. M. **14**:171 (Jan.) 1921.

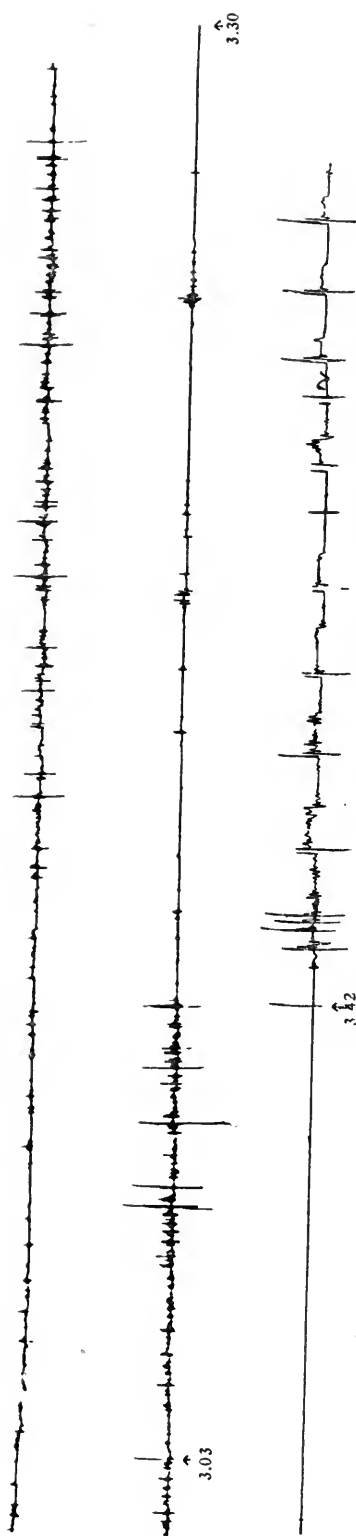


Fig. 1.—A record of the muscular activity March 8, 1921. The experiment began at 3:03 and ended at 3:42.

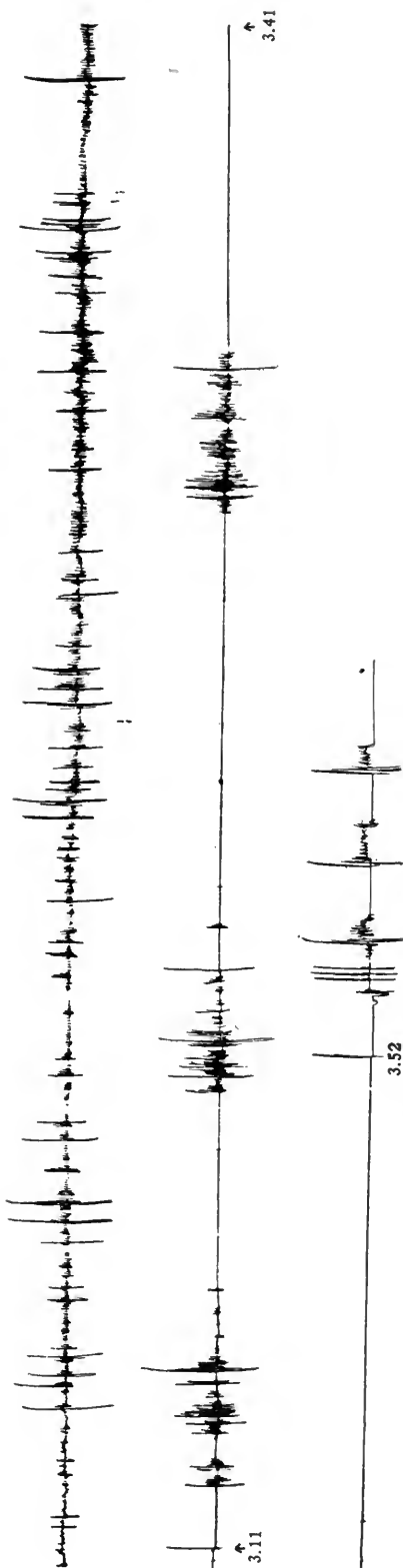


Fig. 2.—The muscular activity March 9, 1921. The experiment began at 3:11 and ended at 3:52.

During the residence in hospital various milk mixtures were tried. It was found that large quantities of carbohydrate were necessary for the child to increase in weight, while large quantities of fat (over 5 per cent.) even with the retention in the diet of the full dose of carbohydrate, caused a loss of weight. The fat in the stools was estimated when the child was on a poor fat diet, a diet with normal amounts of fat in it, and a rich fat diet. I am indebted to Dr. Telfer for the stool examination (table 1).

TABLE 1.—PERCENTAGES OF FAT IN THE DRIED STOOLS

	Period 1 0.8% Fat	Period 2 3.0% Fat	Period 3 5.3% Fat
Neutral fat.....	10.68	5.50	15.26
Free fatty acid (as oleic acid).....	25.34	39.29	48.43
Combined fatty acids.....	28.44	33.23	17.17
Total.....	64.46	78.02	80.86

These figures were arrived at by collecting the feces for several days of each period. Unfortunately, the total excretion of fat was not estimated and compared to the total ingested. The normal amount of fat in the infant's stool is about 30 per cent. So it is clear that in this case, even when on a fat poor diet, there was an enormous excess of fat in the bowel.

TABLE 2.—ESTIMATION OF THE RESPIRATORY EXCHANGE ON VARIOUS FAT DIETS

Date	Liter O ₂ per Hour	Liter CO ₂ per Hour	Respira- tory Quotient	Calories per 24 Hours	Activ- ity*	Weight in Kilo	Diet†
3/ 8/21	2.83	2.88	1.01	343	III	3.85	0.8% fat, 100 c.c.; S., 4 gm.;
3/ 9/21	2.84	2.87	1.01	344	III	3.91	Sl., 4 gm.; 8 times
3/11/21	2.86	2.80	0.97	344	III	3.97	3% fat, 100 c.c.; S., 4 gm.;
3/15/21	3.36	3.40	1.01	407	IV	4.08	Sl., 4 gm.; 8 times
3/17/21	2.76	2.25	0.81	319	I	3.96	5.3% fat, 100 c.c.; 8 times
3/18/21	3.21	2.96	0.92	380	IV	3.91	5.3% fat, 100 c.c.; S., 4 gm.;
							Sl., 4 gm.; 8 times

* Varying degrees of muscular activity are indicated by numbers. The lowest degree of activity being indicated by the numeral I and the highest by the numeral VI. With an activity of I the subject is usually asleep and the movements are minimal, with an activity of VI the subject is moving constantly and probably crying.

† 1% fat = cow's milk containing 1% fat; 3% fat = cow's milk containing 3% fat; 5.3% fat = cow's milk containing 5.3% fat; S. = cane sugar; Sl. = a mixture of starch dextrin and cane sugar.

The infant was fed at three hour intervals and was on the diet indicated in Table 2 for at least twelve hours before each experiment. The Benedict-Talbot respiratory apparatus was used.³ The accuracy of the apparatus was frequently verified by means of control tests with alcohol. In each experiment a preliminary period lasting about thirty minutes was put through. In this period the respiratory quotient was not estimated. It was followed by the experiment proper which

3. Benedict and Talbot: Carnegie Institution of Washington, D. C., 1914.

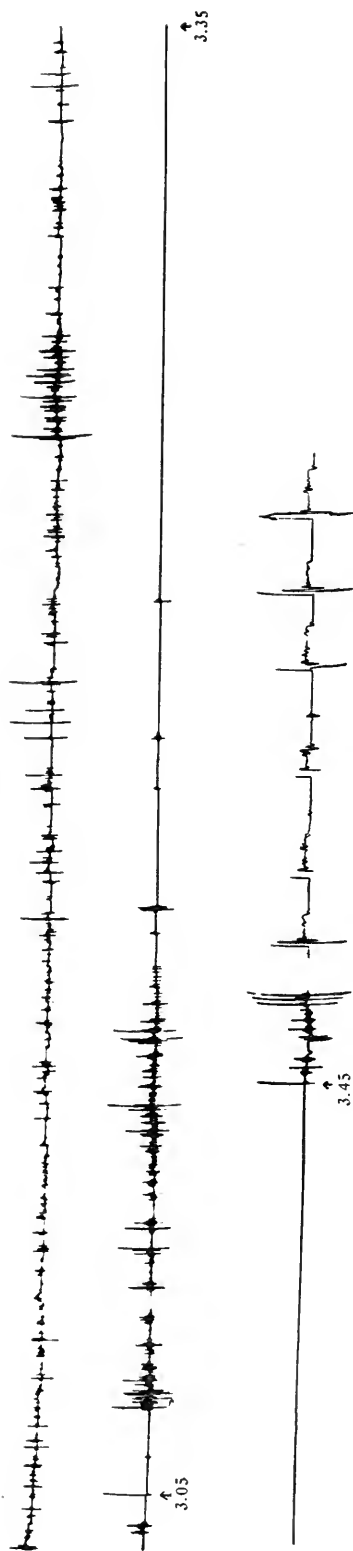


Fig. 3.—The muscular activity March 11, 1921. The experiment began at 3:05 and ended at 3:45.

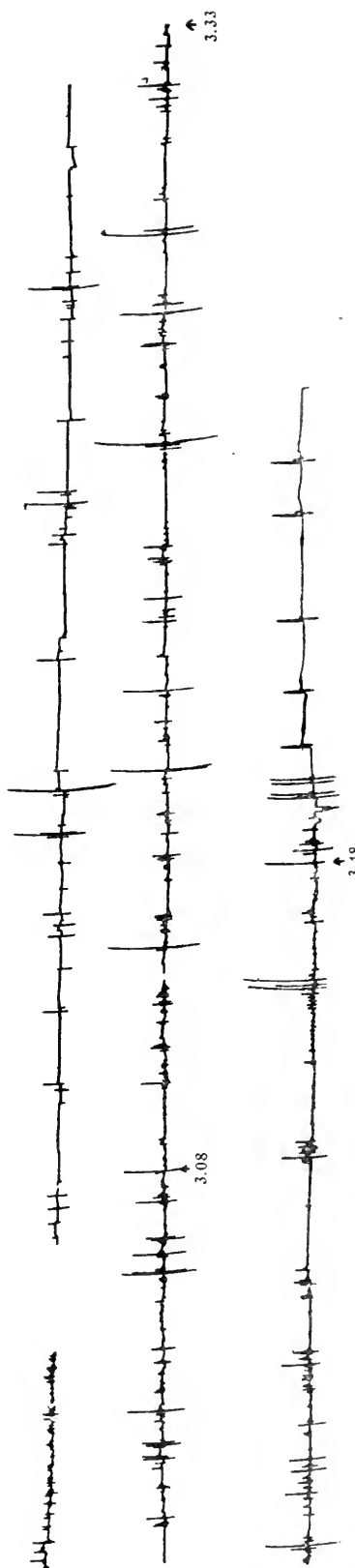


Fig. 4.—The muscular activity March 15, 1921. The experiment began at 3:08 and ended at 3:48.

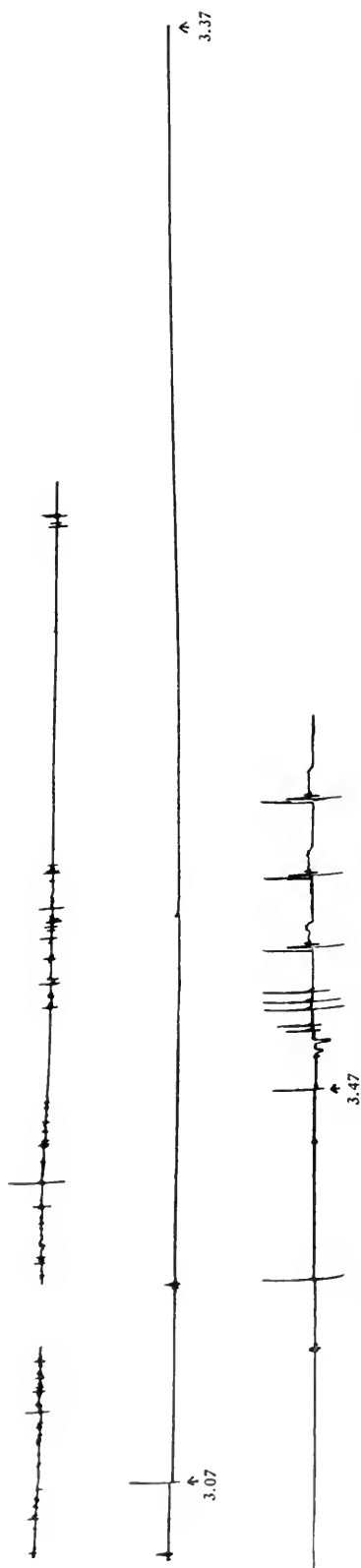


Fig. 5.—The muscular activity March 17, 1921. The experiment began at 3:07 and ended at 3:47.

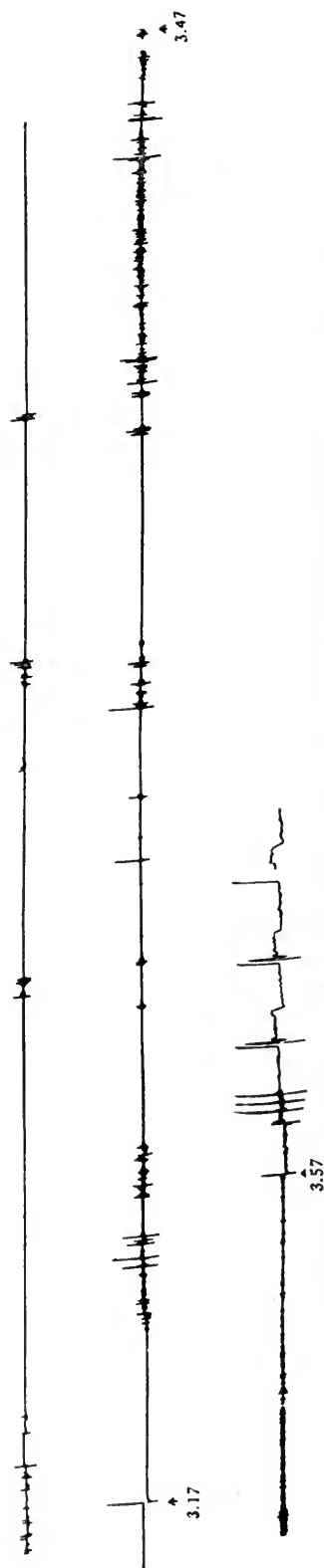


Fig. 6.—The muscular activity March 18, 1921. The experiment began at 3:17 and ended at 3:57.

lasted for from thirty-nine to forty-one minutes. The child was fed from forty-two to fifty-three minutes before the commencement of the experiments to determine the respiratory quotient. Figures 1 to 6 give a graphic record of the muscular activity of the child during each of the experiments. Fortunately almost identical conditions of muscular activity were obtained on March 8, 9 and 11, and also on March 15 and 18.

In the first three experiments in which the activity was the same, the oxygen intake and the carbon dioxide excretion were remarkably constant, and the respiratory quotients also were almost the same, in spite of the fact that in the third experiment three times as much fat was given as in the first two. In the fourth experiment, although the activity was greater the respiratory quotient remained at 1.01. On this day the diet was the same as that on March 11. On March 17 most of the carbohydrate had been cut out of the diet and the fat had been increased to 5.3 per cent. The respiratory quotient fell to 0.81. On March 18 the rich fat diet was maintained but the carbohydrate was brought up to the same strength as was given in the first four experiments. The respiratory quotient on this occasion was 0.92.

Although theoretically a respiratory quotient of 1.0 means that carbohydrate alone is being metabolized, in practice this is not necessarily the case for protein metabolism must always be taking place and this would tend to reduce the respiratory quotient. Probably a respiratory quotient in the neighborhood of 1.0 means that metabolism is being carried on largely at the expense of carbohydrate and that at the same time some carbohydrate is being converted into fat.

In the first four experiments, when moderate amounts of fat were being given (up to 3 per cent.), this is probably what was taking place and these moderate quantities of fat in the diet were no hindrance to the absorption of carbohydrate. In the fifth experiment there is a sudden fall in the respiratory quotient. This may be accounted for in two ways. It will be noted that much more fat and much less carbohydrate were given on that day and the respiratory quotient of 0.81 may be explained either by the diminished quantity of carbohydrate available for combustion or by the excessive quantities of fat causing delay in the absorption of the diminished amount of carbohydrate in the diet. Probably both these factors played their part in the last experiment when the same quantity of fat was given as on the previous day but the amount of carbohydrate in the food was brought up to the same level as in the first experiment. On this occasion the respiratory quotient lay midway between that obtained on the fifth day and on the first 4 days. Probably, therefore, large quantities of fat delayed the absorption of carbohydrate in this case to a moderate degree.

BACTERIOLOGIC STUDIES OF ONE HUNDRED
AND SIXTY-FIVE CASES OF PNEUMONIA
AND POSTPNEUMONIC EMPYEMA IN
INFANTS AND CHILDREN *

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INTRODUCTORY

Extensive bacteriologic studies of pneumonias among adults have established certain cardinal facts.

1. Lobar pneumonia is caused by the pneumococcus—either by one of three fixed biologic types, designated arbitrarily as Types I, II and III, or by a member of the heterogeneous group, called Group IV, which embraces all other strains.¹ Under Type II a series of fixed subtypes has been shown, all closely related to the master strain; these are called atypical Type II.²

2. Under nonepidemic conditions the usual proportionate incidence of infections caused by the different types is about as follows: Type I, 33 per cent.; Type II, 25 per cent.; Type II, atypical, 7 per cent.; Type III, 12 per cent., and Group IV, 22 per cent.³

3. The average mortality of lobar pneumonia caused by pneumococcus Type I is from 25 to 30 per cent. (in cases not treated with serum); by Type II, from 25 to 30 per cent.; by Type II atypical, 25 per cent.; by Type III, from 45 to 50 per cent., and by members of Group IV, from 15 to 20 per cent.

4. The presence of the pneumococcus in the blood stream is of grave prognostic significance. Generally speaking, the mortality is in direct proportion to the severity of the bacteraemia. Invasion of the blood by pneumococcus Type III almost always forecasts a fatal outcome. The elimination of specific soluble substance (precipitin) by way of the kidney is also of prognostic value. The greater the amount of such substance in the urine the more grave the outlook.¹

5. In the mouths of healthy individuals pneumococci of Group IV are common, and of Types II atypical and III not rare. Pneumococci of Types I and II are rarely found in normal individuals.⁴ It follows

* Received for publication, Oct. 17, 1921.

* From the Pneumonia Service of the Boston City Hospital.

1. Avery, Chickering, Cole and Dochez: Monograph No. 7, Rockefeller Institute M. Research, Oct. 16, 1917.

2. Avery, O. T.: J. Exper. M. **21**:804, 1915.

3. Cole, R.: Nelson Loose-Leaf Med. **1**:203, 1920.

4. Stillman, E. G.: J. Exper. M. **24**:651, 1916; Ibid. **26**:513, 1917.

that in the examination of sputum from pneumonia patients the finding of Type I or Type II is most significant, of Type II atypical or Type III something less so, while the finding of a member of Group IV is dubiously interpretable as regards its etiological rôle in the disease.

6. Against pneumococcus Type I a potent therapeutic serum has been prepared which, early and efficiently employed, has notably reduced the mortality for that type.

For bronchopneumonia by very nature no such array of clean-cut facts can be mustered. Bronchopneumonia is not an entity; the term represents a group of pulmonary infections which vary considerably in pathologic detail according to the exciting agent and circumstances of origin. Of the many organisms which may stand in causal relationship to bronchopneumonia the most important are probably the pneumococci, the streptococci, *Staphylococcus aureus*, and the influenza bacillus. The relative frequency of these and other organisms cannot be given. Of the pneumococcus it may safely be said that the fixed types are much less commonly present than in lobar pneumonia. The hemolytic streptococcus is a particularly important organism. Its tendency to produce empyema or other infection of serous membranes and the very high mortality which follows in its train have united to give it a place of unenviable eminence.⁵ Only numerically less important is *Staphylococcus aureus*, which when operative in bronchopneumonia nearly always gives rise to fatal results.⁶

Lobar pneumonia differs in its behavior in the child and in the adult. It is usually a much milder disease in the earlier period, and the death rate is materially lower. Hence, it is clear that the facts which have been established for the disease as it occurs in adult life cannot wholly apply in the case of children.

The relative mildness of lobar pneumonia in childhood may reasonably be explained by one of two hypotheses: (1) the bulk of cases are caused by the less virulent strains of pneumococci, such as are comprised in Group IV; or, (2) the incidence of fixed types being much as for adults, the child opposes to them a better natural resistance than does the average adult.

Definitely to determine which of these hypotheses is correct is a matter of some importance, certainly as regards the carrier problem, if not so much from the standpoint of individual prognosis and treatment. For if most of the pneumonias of childhood are caused by the

5. Cole and MacCallum: J. A. M. A. **70**:1146 (April 20) 1918. MacCallum, W. G.: Monograph No. 10, Rockefeller Institute M. Research, April 16, 1919. Brooks and Cecil: Tr. Assn. Am. Phys. **33**:83, 1918.

6. Chickering and Park: J. A. M. A. **72**:617 (March 1) 1919. Griffith, J. P. C.: Diseases of Infants and Children, Philadelphia **2**: 1920.

common mouth organisms, these small patients are of far less menace as propagators of disease than if they harbor the fixed, and for adults much more virulent, fixed types.

In short, the particular problem which offers itself for solution is to determine the degree of parallelism between the etiology of the pneumonias of childhood and that of the pneumonias of adult life. Such a comparison must be easier to initiate in the case of lobar pneumonia than in the case of lobular pneumonia, but the occurrence in children of the most dreaded organisms associated with adult bronchopneumonia (such, for example, as the hemolytic streptococcus) would have a similar bearing on the carrier problem as would the occurrence of the fixed types of pneumococci.

The question of the parallelism of etiology in these two periods of life must still be considered as an open one. It is true that such few bacteriologic studies as have been reported for the pneumonias of infancy and childhood have led to the statement that the common mouth forms of pneumococci (Group IV) are largely responsible for these diseases during that period, that the fixed types are relatively infrequent, and specifically that Type I pneumococcus is comparatively rare. In reviewing the studies from which these statements are derived, however, one is struck with the numerical inadequacy of the data. Too few cases have been reported to admit of any general definite conclusions.

The studies which are reported in this paper are intended to furnish additional data along these lines. One hundred and sixty-five patients, 12 years of age or younger, ill with lobar pneumonia, bronchopneumonia, or complications of these diseases, have been investigated. The results of these studies are presented in the spirit of suggestion rather than of finality, and with the hopes that further studies may be undertaken in a field that promises to be important.

MATERIALS AND METHODS

These studies are based on sputum examinations, blood cultures, cultures from pleural fluids, or from the lung itself, and in rare instances from spinal fluids. It has not been possible to attempt a study of the precipitin reaction in the urine.

Sputum.—There has been, on the whole, less difficulty in securing sputum for examination than might have been expected. The first method we employed was to introduce a sterile rubber catheter (No. 18 or 20 French) against the patient's pharyngeal wall, taking care to avoid the tongue, tonsils and buccal mucous membrane. The active gag reflex attendant on this procedure was usually productive of sufficient sputum to fill the eye of the catheter. This material was at once washed into 1 or 2 c.c. of sterile broth or salt solution, the

tube shaken to secure as even an emulsion as possible, and a sample introduced into the peritoneum of a white mouse. Any remaining material could be used for smear preparations. Subsequently it appeared that a medium-sized sterile cotton swab was quite as efficient as the catheter on which to catch the sputum, besides obviating the necessity of repeated sterilizations.

Cultures from the peritoneal exudate and heart's blood of the mouse have been handled in the usual manner.¹ In every instance the organism (or organisms) reported has been obtained by means of mouse passage; it has not been feasible to make direct plate cultures of the sputum as obtained.

Blood cultures have been made in suitable cases. Small superficial veins have constituted a real and frequent difficulty. To withdraw sufficient blood may require repeated attempts, and besides the attendant discomfort, much manipulation greatly increases the liability of contamination. In consequence we have met with some failures, and in other cases we have not even attempted the procedure, when, *ceteris paribus*, we should have wished these data. In other cases in which the disease has been obviously very mild or well advanced toward convalescence a blood culture seemed* superfluous.

In infants we have occasionally resorted to puncture of the longitudinal sinus through the open fontanel. In marasmic and desiccated infants, however, we have sometimes feared to withdraw even the amount of blood necessary for culture. Hence the infrequency of this procedure.

The blood cultures were made in flasks, from 3 to 4 c.c. blood to 50 c.c. of a beef infusion broth, p_H , 7.8. Cultures were incubated at 37 C. for five or six days before being discarded as sterile. In the event of growth, the usual means were employed to identify the organism.

Lung Punctures.—Although in the pathologic sense no untoward effects are to be anticipated from the puncture of a solid lung, I am reluctant to tap the chest unless there is suspicion of fluid. At best, it is a somewhat painful procedure, and often excites in the child patient a terror which for several days to come reawakens with every appearance of the physician. In the event of a dry tap, when the needle has entered the lung, it has been our habit to wash out the tip in a tube of sterile broth. Thus not infrequently we have obtained a culture direct from the seat of the pathologic process. A few lung cultures have been made by this means directly after death.

Pleural Fluids.—No matter what the character of the fluid was, we have cultured it directly into broth. Further plate cultures from this parent broth culture have been made as indicated.

Spinal fluids were taken only from the few cases in which there was reasonable suspicion of meningeal involvement. Cultures were made into broth, on solid medium, or both.

BACTERIOLOGY

Ninety-eight cases of lobar pneumonia, fifty-two cases of broncho-pneumonia, and fifteen cases of postpneumonic empyema have been studied. Those cases of lobar or of bronchopneumonia in which empyema developed under observation have been classified in this schedule under the name of original disease. It should be stated that in making the differential diagnosis between lobar and lobular pneumonia we have been guided solely by clinical and roentgenologic findings, and in no instance by the type of organism recovered from the case.

The bacteriologic findings in the above mentioned cases are fully shown in Table I, which gives the organism or organisms isolated in each, and the particular source of such findings, the age, principal complications, and result in each case.

TABLE 1.—BACTERIOLOGICAL FINDINGS IN ONE HUNDRED AND SIXTY-FIVE CASES OF PNEUMONIA AND EMPYEMA IN INFANTS AND CHILDREN

Case No.	Age	Diagnosis	Organism	Sputum	Blood	Lung	Pleural Fluid	Result	Remarks
19	10	Lobar	Pneumococcus I	+	Rec.	
22	9	Lobar	Pneumococcus I	+	Rec.	
23	10	Lobar	Pneumococcus I	+	Rec.	
65	4	Lobar	Pneumococcus I	+	Rec.	
131	1 ⁸ / ₁₂	Lobar	Pneumococcus I	+	Rec.	
116	5	Lobar	Pneumococcus I	+	S.*	Rec.	
101	1 ² / ₁₂	Lobar	Pneumococcus I	+	S.	Rec.	
98	11	Lobar	Pneumococcus I	+	S.	Rec.	Urine precipitin +
72	8	Lobar	Pneumococcus I	+	..	+	..	Rec.	Serum treatment
73	9	Lobar	Pneumococcus I	+	..	+	..	Rec.	Serum treatment
45	7	Lobar	Pneumococcus I	+	..	Rec.	Serum treatment
68	7	Lobar	Pneumococcus I	..	+	Died	Laryngeal diphtheria complicating..
78	5	Lobar	Pneumococcus I	..	+	Rec.	
80	11	Lobar	Pneumococcus I	..	+	Rec.	
75	6	Lobar	Pneumococcus I	+	Rec.	Empyema; operation
77	12	Lobar	Pneumococcus I	+	Rec.	Empyema; operation
79	2 ⁴ / ₁₂	Lobar	Pneumococcus I	+	Rec.	Empyema; operation
129	10 ¹⁰ / ₁₂	Lobar	Pneumococcus I	+	Died	Empyema; operation
74	6	Lobar	Pneumococcus I	..	+	+	+	Rec.	Empyema; operation
69	4 ⁹ / ₁₂	Lobar	Pneumococcus I	+	Died	Empyema; operation
123	7	Lobar	Pneumococcus I	..	+	+	+	Empyema; operation
112	5	Lobar	Pneumococcus I	+	Rec.	Empyema; operation
107	4	Lobar	Pneumococcus I	—	+	+	+	Rec.	Empyema; operation
			Pneumococcus IV	+	—	—	—		
71	7	Lobar	Pneumococcus I	—	+	Rec.	Empyema; operation
			Pneumococcus IV	+	+		
115	11	Lobar	Pneumococcus I	—	S.	..	+	Empyema; operation
			Strep. viridans	+		
20	6	Lobar	Pneumococcus I	+	Rec.	
21	9	Lobar	Pneumococcus I	+	+	..	S.	Rec.	
			Pfeiffer	+	+		
110	7	Lobar	Pneumococcus I	+	S.	..	+	Rec.	Spinal fluid sterile; pneumothorax; diphtheria; scarlet fever; operation
			Pfeiffer	+	—		
54	6	Lobar	Pneumococcus I	+	S.	Rec.	

* Sterile.

† Contaminated.

‡ Reinfection, three weeks later.

§ Mouse lived.

TABLE 1.—BACTERIOLOGICAL FINDINGS IN ONE HUNDRED AND SIXTY-FIVE CASES OF PNEUMONIA AND EMPYEMA IN INFANTS AND CHILDREN.—(Continued)

Case No.	Age	Diagnosis	Organism	Sputum	Blood	Lung	Pleural Fluid	Result	Remarks
3	10	Lobar	Pneumococcus II	+	S.	S.	..	Rec.	
119	3	Lobar	Pneumococcus II	+	Rec.	
11	8	Lobar	Pneumococcus IIa	+	Rec.	
70	10	Lobar	Pneumococcus III	+	†	Rec.	
105	6	Lobar	Pneumococcus III	+	S.	Rec.	
1	9	Lobar	Pneumococcus III	+	..	S.	..	Rec.	
			Pfeiffer	+	Rec.	
50	9	Lobar	Pneumococcus III	+	S.	Rec.	
			Pfeiffer	+	Rec.	
51	12	Lobar	Pneumococcus III	+	S.	Rec.	
			Pfeiffer	+	Rec.	
5	12	Lobar	Pneumococcus III	+	S.	Rec.	
			Pfeiffer	+	Rec.	
18	12	Lobar	Pneumococcus III	+	Rec.	
			Strep. viridans	+	Rec.	
7	5	Lobar	Pneumococcus IV	+	Rec.	
9	6	Lobar	Pneumococcus IV	+	Rec.	
10	8	Lobar	Pneumococcus IV	+	S.	Rec.	
12	7	Lobar	Pneumococcus IV	+	Rec.	
13	9	Lobar	Pneumococcus IV	+	Rec.	
15	12	Lobar	Pneumococcus IV	+	Rec.	
16	6	Lobar	Pneumococcus IV	+	Rec.	
56	2 ¹⁰ / ₁₂	Lobar	Pneumococcus IV	+	Rec.	
57	1 ⁸ / ₁₂	Lobar	Pneumococcus IV	+	Rec.	
59	8 ⁸ / ₁₂	Lobar	Pneumococcus IV	+	Rec.	
96	6	Lobar	Pneumococcus IV	+	S.	Rec.	
97	12	Lobar	Pneumococcus IV	+	S.	Rec.	
62	2	Lobar	Pneumococcus IV	+	Rec.	
64	6	Lobar	Pneumococcus IV	+	Rec.	
99	2	Lobar	Pneumococcus IV	+	S.	Rec.	
99½	..	Lobar	Pneumococcus IV	+	Rec.	
100	4	Lobar	Pneumococcus IV	+	S.	Rec.	
103	12	Lobar	Pneumococcus IV	+	S.	Rec.	
104	6	Lobar	Pneumococcus IV	+	S.	Rec.	
105	5	Lobar	Pneumococcus IV	+	S.	Rec.	
109	4	Lobar	Pneumococcus IV	+	S.	Rec.	
111	7	Lobar	Pneumococcus IV	+	S.	Rec.	
113	11	Lobar	Pneumococcus IV	+	S.	Rec.	
120	3	Lobar	Pneumococcus IV	+	Rec.	
121	3	Lobar	Pneumococcus IV	+	Rec.	
124	1 ⁵ / ₁₂	Lobar	Pneumococcus IV	+	Rec.	
127	2 ⁸ / ₁₂	Lobar	Pneumococcus IV	+	S.	Rec.	
126	9	Lobar	Pneumococcus IV	+	S.	S.	..	Rec.	
67	1 ⁵ / ₁₂	Lobar	Pneumococcus IV	+	..	Rec.	
76	7	Lobar	Pneumococcus IV	+	Rec.	Empyema; operation
66	8	Lobar	Pneumococcus IV	+	..	Died	Lung puncture postmortem
130	1 ⁸ / ₁₂	Lobar	Pneumococcus IV	..	†	+	..	Died	Lung culture postmortem
4	2	Lobar	Pneumococcus IV	+	†	Rec.	
			Pfeiffer	+	Rec.	
6	6 ⁸ / ₁₂	Lobar	Pneumococcus IV	+	Rec.	
			Pfeiffer	+	Rec.	
14	12	Lobar	Pneumococcus IV	+	Rec.	
			Pfeiffer	+	Rec.	
24	9	Lobar	Pneumococcus IV	+	Rec.	
			Pfeiffer	+	Rec.	
60	2	Lobar	Pneumococcus IV	+	Rec.	
			Pfeiffer	+	Rec.	
118	4	Lobar	Pneumococcus IV	+	S.	+	..	Rec.	
			Pfeiffer	+	..	+	..	Rec.	
102	7	Lobar	Strep. hemolyticus	§	S.	+	+	Died	Empyema; operation; general peritonitis
48	10	Lobar	Strep. hemolyticus	+	S.	Rec.	
			Strep. viridans	+	Rec.	
			Pfeiffer	+	Rec.	
17	6	Lobar	Strep. viridans	+	Died	Laryngeal diphtheria complicating
			Pfeiffer	+	Rec.	
2	7	Lobar	Strep. viridans	+	Rec.	
25	3	Lobar	Strep. viridans	+	Rec.	
8	11	Lobar	Strep. viridans	+	Rec.	
49	3	Lobar	Strep. viridans	+	Rec.	
			Pfeiffer	+	Rec.	

TABLE 1.—BACTERIOLOGICAL FINDINGS IN ONE HUNDRED AND SIXTY-FIVE CASES OF PNEUMONIA AND EMPYEMA IN INFANTS AND CHILDREN.—(Continued)

Case No.	Age	Diagnosis	Organism	Sputum	Blood	Lung	Pleural Fluid	Result	Remarks
135	7	Lobar	Unknown	S.	..	Rec.	
136	1 5/12	Lobar	Unknown	S.	..	Rec.	
137	11	Lobar	Unknown	S.	..	Rec.	
138	10	Lobar	Unknown	S.	..	Rec.	
139	7	Lobar	Unknown	S.	..	Rec.	
140	8	Lobar	Unknown	..	S.	Rec.	
141	6	Lobar	Unknown	Rec.	
142	3	Lobar	Unknown	S.	..	Rec.	
143	1 7/12	Lobar	Unknown	..	S.	Rec.	
144	12	Lobar	Unknown	Rec.	
145	12	Lobar	Unknown	Rec.	
146	8	Lobar	Unknown	..	+	..	S.	Rec.	
147	9	Lobar	Unknown	..	S.	Rec.	
148	3	Lobar	Unknown	..	S.	Rec.	
133	10	Lobar	Unknown	..	S.	Rec.	
33	8	Broncho	Pneumococcus I	+	..	S.	..	Rec.	
36	9	Broncho	Pneumococcus I	+	Rec.	
95	2 6/12	Broncho	Pneumococcus I	..	+	..	+	Died	
			Pfeiffer	..	—	..	+		
84	7	Broncho	Pneumococcus II	+	—	S.	..	Died	
			Strep. hemolyticus	—	+		
42	9/12	Broncho	Pneumococcus Iia	+	0	S.	..	Died	Lung puncture postmortem
30	1 3/12	Broncho	Pneumococcus III	+	Rec.	
35	8	Broncho	Pneumococcus III	+	Rec.	
			Pfeiffer	+		
58	1 4/12	Broncho	Pneumococcus IV	+	Rec.	
29	1 11/12	Broncho	Pneumococcus IV	+	Died	Spinal fluid +; pneumococcus meningitis complicating
117	3	Broncho	Pneumococcus IV	+	Rec.	
82	8/12	Broncho	Pneumococcus IV	+	..	Died	Lung puncture postmortem
94	3	Broncho	Pneumococcus IV	+	..	Died	Lung puncture postmortem
91	2	Broncho	Pneumococcus IV	+	Died	Empyema; operation
47	1	Broncho	Pneumococcus IV	+	Rec.	
122	2	Broncho	Pneumococcus IV	+	Rec.	
134	3	Broncho	Pneumococcus IV	+	Rec.	
28	7/12	Broncho	Pneumococcus IV	+	Rec.	
			Pfeiffer	+		
31	4	Broncho	Pneumococcus IV	+	Rec.	
			Pfeiffer	+		
32	1 6/12	Broncho	Pneumococcus IV	+	Rec.	
			Pfeiffer	+		
34	2	Broncho	Pneumococcus IV	+	Died	
			Pfeiffer	+		
55	11	Broncho	Pneumococcus IV	+	Rec.	
			Pfeiffer	+		
38	2	Broncho	Pneumococcus IV	+	Imp.	
			Pfeiffer	+		
26	1 2/12	Broncho	Pneumococcus IV	+	Rec.	
			Strep. hemolyticus	+		
			Pfeiffer	+		
46	8	Broncho	Pneumococcus IV	+	Rec.	
			Strep. hemolyticus	+		
			Pfeiffer	+		
85	1 6/12	Broncho	Pneumococcus IV	+	..	Died	
			Staph. aureus	+	..		
90	1 4/12	Broncho	Pneumococcus IV	+	..	Died	
			Strep. hemolyticus	+	..		
61	8/12	Broncho	Strep. hemolyticus	+	Died	
92	1	Broncho	Strep. hemolyticus	+	Died	Empyema; operation
93	11	Broncho	Strep. hemolyticus	+	Died	Empyema; operation
40	9/12	Broncho	Strep. hemolyticus	+	Died	
			Pfeiffer	+		
41	6/12	Broncho	Strep. hemolyticus	+	Died	
			Pfeiffer	+		
27	1 5/12	Broncho	Strep. hemolyticus	+	Died	
			Strep. viridans	+		
86	7	Broncho	Strep. hemolyticus	—	+	Rec.	Empyema; operation
			Staph. aureus	+	+		
			Yeast	+	+		

TABLE 1.—BACTERIOLOGICAL FINDINGS IN ONE HUNDRED AND SIXTY-FIVE CASES OF PNEUMONIA AND EMPYEMA IN INFANTS AND CHILDREN—(Continued)

Case No.	Age	Diagnosis	Organism	Sputum	Blood	Lung	Pleural Fluid	Result	Remarks
39	6	Broncho	Strep. viridans	+	Rec.	Multiple abscess
37	2 ⁶ / ₁₂	Broncho	Strep. viridans Pfeiffer	+	Med.	
83	8	Broncho	Staph. aureus	..	+	+	..	Lived	
89	4	Broncho	Staph. aureus	+	..	+	..	Died	
44	1 ⁶ / ₁₂	Broncho	Staph. aureus	+	..	Died	
81	4 ⁶ / ₁₂	Broncho	Staph. aureus	+	..	+	..	Died	Died
43	1 ⁵ / ₁₂	Broncho	Pneumococcus IV Staph. aureus	+	Died	
88	1	Broncho	Strep. viridans Staph. albus	+	..	+	..	Died	
128	1 ⁶ / ₁₂	Broncho	Pfeiffer	+	Died	
132	4	Broncho	Unknown	..	S.	S.	..	Rec.	
149	10	Broncho	Unknown	..	S.	Rec.	Spinal fluid sterile
150	1 ³ / ₁₂	Broncho	Unknown	..	S.	Rec.	
151	2	Broncho	Unknown	S.	..	Died	
152	2	Broncho	Unknown	+	..	Died	
153	7 ¹² / ₁₂	Broncho	Unknown	Died	
154	2 ⁶ / ₁₂	Broncho	Unknown	..	S.	Died	
155	2 ¹² / ₁₂	Broncho	Unknown	..	S.	Died	
156	2 ⁶ / ₁₂	Broncho	Unknown	..	S.	Died	
157	5	Broncho	Unknown	S.	..	Rec.	
158	3	Postpneumonic empyema	Pneumococcus I	+	Rec.	Operation
159	11	Postpneumonic empyema	Pneumococcus I	+	Rec.	Operation
160	2	Postpneumonic empyema	Pneumococcus I	+	Rec.	Operation
161	9	Postpneumonic empyema	Pneumococcus I	+	Rec.	Operation
162	10	Postpneumonic empyema	Pneumococcus I	+	Rec.	Operation
163	8	Postpneumonic empyema	Pneumococcus I	+	Rec.	Operation
164	4	Postpneumonic empyema	Pneumococcus I	+	Rec.	Operation
165	5	Postpneumonic empyema	Pneumococcus I	+	Died	Operation
166	2	Postpneumonic empyema	Pneumococcus I	+	Died	Operation
167	7	Postpneumonic empyema	Pneumococcus I	+	Rec.	Operation
168	9	Postpneumonic empyema	Pneumococcus I	+	Rec.	Operation
169	3	Postpneumonic empyema	Pneumococcus untyped	+	Rec.	Operation
170	3	Postpneumonic empyema	Strep. hemolyticus	+	Rec.	Operation
171	6	Postpneumonic empyema	Pneumococcus IV	+	Rec.	Operation
172	4	Postpneumonic empyema	Staph. aureus	+	Rec.	Operation

LOBAR PNEUMONIA

Sputum Examinations.—Seventy-three examinations were made. The findings of pneumococcus types in these sputums is shown in Table 2, arranged according to age groups, and indicating the mortality for each type within the age group.

TABLE 2.—PNEUMOCOCCUS TYPES AND MORTALITY IN SPUTUM IN SEVENTY-THREE CASES OF LOBAR PNEUMONIA IN INFANTS AND CHILDREN

Organism	First 2 Years			2 to 5 Years			6 to 12 Years			Totals		
	Percentage			Percentage			Percentage			Percentage		
	No.	Group	Mortality	No.	Group	Mortality	No.	Group	Mortality	No.	Total	Mortality
Pneumococcus I...	2	22.2	0	1	6.25	0	11	20.9	0	14	19.1	0
Pneumococcus II...	0	0	0	1	6.25	0	1	2.0	0	2	2.7	0
Pneumococcus IIa	0	0	0	0	0	0	1	2.0	0	1	1.4	0
Pneumococcus III	0	0	0	0	0	0	7	14.5	0	7	9.6	0
Pneumococcus IV	7	77.8	14.1	10	62.5	0	18	37.5	0	35	48.0	2.8
Other than pneumococcus.....	0	0	0	2	12.5	0	5	10.1	20	7	9.6	14.0
No result.....	0	0	0	1	6.25	0	6	12.0	0	7	9.6	0
Totals.....	9	0	11.0	16	100.0	0	48	100.0	2	73	100.0	2.7

In attempting to interpret these results we are confronted with the difficulties elsewhere mentioned. The finding in the sputum alone of a Group IV pneumococcus is always shadowed by the doubt as to whether it is really the pathogenic agent in the given case. One may sometimes doubt the significance of an atypical Type II or Type III pneumococcus so recovered. But the finding of a Type I or Type II is nearly always significant. The greater the number of Group IV's isolated, the more difficult are the results of estimation. In any series the error will almost invariably be on the side of understatement of the occurrence of fixed types rather than the reverse. The difficulty is, of course, to determine the degree of error. In this series we have been able actually to prove error in the sputum findings in only three cases; in these, blood, lung or pleural fluid showed the presence of a type pneumococcus which we had failed to isolate from the sputum. In fifty-seven cases, however, the only positive bacteriologic evidence was derived from the sputum. Hence, in passing any sort of judgment on the general dependability of our results our sole criterion is in the nature of indirect evidence, namely, as to how the findings in these children compare with the findings in a parallel series of cases in adults.

As regards the finding of other organisms than pneumococcus in an occasional sputum, I am not aware of any evidence to warrant the belief that such are ever the cause of lobar pneumonia. It is worthy of comment that Pfeiffer's bacillus is commonly present in the sputum of these children with lobar pneumonia. It has been found fourteen times, in association with pneumococcus, in this series of seventy-three sputum examinations.

Blood Cultures.—Forty-three blood cultures were made, representing 43.8 per cent. of the total cases studied. Six, or about 14 per cent., of these forty-three cultures were positive. Of the remainder four were contaminated; the others were sterile. All the positive cultures were of pneumococcus Type I. Only one of these patients died; in this case a laryngeal diphtheria complicated the pneumonia. Of the thirty-seven cases in which the blood was negative, two patients died; one of these had an uncomplicated pneumonia; the other died from empyema and general peritonitis which followed the pneumonia.

Lung punctures were performed in twenty cases (20.3 per cent. of the cases studied). With two exceptions these punctures were done during life. In ten cases the cultures were sterile. Of the 50 per cent. positive, six showed a pure culture of pneumococcus Type I, three a pure culture of pneumococcus Group IV, and one a mixed growth of pneumococcus Group IV and Pfeiffer's bacillus.

Pleural Fluids.—Fluid was found in the pleura in sixteen cases, or 16.3 per cent. of those studied. In three cases (3 per cent.) this fluid was sterile. The remaining thirteen cases (13.3 per cent.) represent frank empyema. Of the thirteen empyemas, eleven were caused by pneumococcus Type I, one by pneumococcus Group IV, and one by *Streptococcus haemolyticus* (Case 102)..

Experience has shown that mixed pneumococcus infections are almost unknown. One, and only one, type is operative in a given individual at a given time. On this basis it has seemed only reasonable to attribute to the type pneumococcus recovered from the pleural pus the etiologic rôle in the antecedent pneumonia, though no supporting data were available, or in particular, even when the sputum finding was in contradiction.

On the other hand, it is well known that infection with *Streptococcus haemolyticus* is not uncommonly superimposed on pneumococcus pneumonia,⁷ and, though proof is wanting, I am inclined to believe that such was the course of events in the one case which showed a streptococcus empyema.

Further observations on the bacteriology of empyema are reserved for a later portion of the paper.

BRONCHOPNEUMONIA

Sputum Examinations.—These were made in thirty-one of the fifty-two cases studied. The sputum bacteriology of these thirty-one cases is given in Table 3.

7. Clendenning, L.: Am. J. M. Sc. **156**:575, 1918.

TABLE 3.—SPUTUM BACTERIOLOGY IN THIRTY-ONE CASES OF BRONCHOPNEUMONIA IN INFANTS AND CHILDREN

	Cases	Deaths	Percentage Incidence	Percentage Mortality
<i>Pneumococcus</i> Type I.....	3	1	9.7	33.3
<i>Pneumococcus</i> Type II.....	1	1	3.2	100.0
<i>Pneumococcus</i> Type II atypical.....	1	1	3.2	100.0
<i>Pneumococcus</i> Type III.....	2	0	6.4	0.0
<i>Pneumococcus</i> Group IV.....	12	2	38.7	16.7
<i>Streptococcus hemolyticus</i>	4	4	12.9	100.0
<i>Streptococcus viridans</i>	2	1	6.4	50.0
<i>Staphylococcus aureus</i>	2	1	6.4	50.0
<i>B. influenzae</i> (e other organism).....	11	..	35.4	
Other mixed bacteriology.....	4	1	12.9	25.0
Totals.....	31	12	38.7

It is known that any and all of these organisms may stand in etiologic relationship to bronchopneumonia. In three cases only is there confirmatory evidence actually to establish such relationship. The status of the other findings must in the last analysis remain conjectural, and unfortunately we have no standard with which to compare them. It is noteworthy that while the percentage figures show a decrease from lobar pneumonia in the total occurrence of fixed types, the reduction is largely at the expense of Type I, and that the increase in the occurrence of Group IV is relative rather than absolute. Other organisms than pneumococcus appear prominently in the list.

Blood Cultures.—Eleven cultures were made, representing about 21 per cent. of the cases studied. Of these three, or 27.2 per cent. were positive, the remainder were sterile. All the positive cultures showed pure growths—one of pneumococcus Type I, one of *Staphylococcus aureus*, and one of *Streptococcus haemolyticus*. From the last mentioned case, a Type II pneumococcus had been isolated from the sputum, and possibly the streptococcus represents a superimposed infection. The patient with pneumococcus septicemia also developed empyema. Both these patients died. The child with staphylococcus septicemia apparently recovered from the immediate infection, but has since become a confirmed invalid, suffering from multiple osteomyelitis.

Lung punctures were performed in eighteen, or 34.6 per cent. of the fifty-two cases. Positive cultures were obtained in nine (50 per cent.). The findings in these cases were as follows: pneumococcus Group IV, 2 cases; *Staphylococcus aureus*, 4 cases; pneumococcus, Group IV, plus *Staphylococcus aureus*, 1 case; pneumococcus Group IV, plus *Streptococcus haemolyticus*, 1 case; *Staphylococcus albus*, plus *B. Influenzae*, 1 case. Two of these punctures were performed postmortem. The only child among the entire series who lived was that from whom *Staphylococcus aureus* was obtained in pure culture—the same child mentioned above in whose blood this organism was present. There were only three recoveries among the nine cases in which lung punc-

tures were negative. There is little, then, to suggest that negative results in lung punctures warrant a more favorable prognosis.

POSTPNEUMONIC EMPYEMA

Fifteen cases admitted to the wards have been studied. While a large majority probably followed lobar pneumonia, the type of antecedent infection remains in some doubt, and I have preferred to classify the cases under the general heading "postpneumonic." In each of these cases a pure culture was obtained from the pleural pus. Of the fifteen cases, eleven showed pneumococcus Type I, one showed *Streptococcus haemolyticus*, one pneumococcus Group IV, one *Staphylococcus aureus*, and one a pneumococcus which was not typed.

DISCUSSION

As already stated, no claim is made that the organism isolated is in every case the agent of the disease. The difficulty of interpretation of the sputum bacteriology has already been fully discussed. But so far as concerns lobar pneumonia we have an indirect check on the general reliability of our results in the comparison of our cases with a parallel series in adults. The bulk of our examinations were made in the first five months of 1921. In Table 4 I have compared the percentage figures for the different types in our series with similar figures for 151 cases in adults admitted to this hospital during the same period.

TABLE 4.—COMPARISON OF INCIDENCE OF PNEUMOCOCCUS TYPES IN LOBAR PNEUMONIA IN ADULTS AND IN CHILDREN

	Adults; Percentage of 151 Cases	Infants and Children; Percentage of 98 Cases
Pneumococcus Type I.....	37.7	29.6
Pneumococcus Type II (including atypical).....	8.0	3.0
Pneumococcus Type III.....	13.2	7.1
Pneumococcus Group IV.....	24.5	35.7
Undetermined.....	16.5	25.7

It will be noted that in adults pneumococcus Type I has been particularly prevalent, that pneumococci of Group IV have been very common, that Type III has occurred with about average frequency, but that there has been a notable paucity of Type II. If we reverse the positions of Type I and Group IV in children, the same order of frequency then follows. More important than that, the actual percentage figures in the two series, type for type, are not so greatly at variance. The parallelism is sufficiently strong to suggest not only that the results we have obtained in our younger patients are, in the main, tolerably accurate, but that the etiology of lobar pneumonia in infants and chil-

dren follows quite closely the etiology of that disease in adults in a given place and season.

It is somewhat more difficult to institute a comparison of our results with those published by other authors for pneumonia in infants and children. For the most part these studies have not attempted to segregate the two varieties of pneumonia—a thing often difficult to do, but from the standpoint both of prognosis and etiology of considerable importance. The more important articles may, however, be reviewed.

Wollstein and Benson,⁸ in a series of fifty cases of pneumonia, chiefly in infants, and chiefly lobular, found pneumococcus Type I in 8 per cent., Type II in 12 per cent., Type III in none, and Group IV in 60 per cent. A number of infections were of mixed character.

Mitchell,⁹ in a series of ninety cases in infants and children, chiefly lobar, found pneumococci of Group IV in no less than 74.4 per cent. of the cases of lobar pneumonia, which comprised the greater proportion of his cases.

Pisek and Pease,¹⁰ in a series of forty-eight cases of pneumonia in infants and small children, of whom more than half were of the lobar variety, found pneumococcus Type I in 15.2 per cent., Type II in 20 per cent., Type III in 5.6 per cent., and Group IV in 26.7 per cent. The bacteriology of the remaining 32.5 per cent. could not be determined. These figures, though of so small a series, accord more nearly with our own, and with the figures usual in adults, than do the others.

If the figures of these authors be thrown together, it will be found that of 188 cases of lobar and lobular pneumonia, 62.5 per cent. appear to be associated with pneumococci of Group IV, while only 25 per cent. showed the presence of fixed types. Applying the same process to our own 165 cases of pneumonia and postpneumonic empyema, it will be seen that pneumococci of Group IV were present in 33.3 per cent., while 34.6 per cent. showed the presence of fixed types. The approximate ratios of fixed types to heterogeneous strains in the two series are respectively 1:2.5 and 1:1.

Our studies suggest, then, that in pneumonia in infants and children—in particular the lobar form—the fixed types of pneumococcus are relatively much more common than we have been led to believe. That these small patients are at least potentially more important as carriers of disease than has been thought, follows in course. Indeed, several concrete illustrations of this point may be adduced. Thus, Case 131 is the sister of Case 107; they were admitted within a short time of each other, both suffering from lobar pneumonia caused by pneumo-

8. Wollstein and Benson: *Am. J. Dis. Child.* **12**:254 (Sept.) 1916.

9. Mitchell: *Penn. M. J.* **20**:343, 1917.

10. Pisek and Pease: *Am. J. M. Sc.* **151**:14, 1916.

coccus Type I. A third child is reported to have died at home with pneumonia between the times of the two admissions. Case 98 was the original case in his family; he was admitted with lobar pneumonia, pneumococcus Type I. A few days later his brother, a young adult, was admitted with the same disease, caused by the same type. Case 112 was in the hospital at the same time as her father; both suffered from lobar pneumonia caused by the same type of pneumococcus. Not many illustrations of this sort are needed to establish the point that the same rigid precautions should be carried out with pneumonia in childhood as in adults.

It appears that in general the child has a better natural immunity to his infecting type of pneumococcus than does the average adult. This is well shown in Table 5. From the few positive blood cultures we have obtained it is unfair to draw conclusions; it is suggested, however, that invasion of the blood is of less serious import in the child than in the adult.

TABLE 5.—COMPARATIVE MORTALITY FOR LOBAR PNEUMONIA IN ADULTS AND CHILDREN ACCORDING TO TYPES OF PNEUMOCOCCI

Type	Percentage Mortality, Adults	Percentage Mortality, Children
Pneumococcus Type I.....	30.0	7.9
Pneumococcus Type II.....	16.6	0
Pneumococcus Type III.....	75.0	0
Pneumococcus Type IV.....	10.8	5.7

It should be noted that type for type, with one exception, there is a higher mortality recorded for bronchopneumonia than for lobar pneumonia (Figs. 1 and 2). This exception is pneumococcus Type III. Although it was found in nine lobar or lobular pneumonia cases, there were no deaths, a fact of exceptional interest, since the death rate for this type in adults has been extremely high. Doubtless, the generally higher mortality in bronchopneumonia is largely due to the conditions of origin and circumstances of that disease, which in the cases studied has been very rarely primary.

Streptococcus haemolyticus and *Staphylococcus aureus* appear as important agents in the bronchopneumonias which we have studied. Responsibility for this disease is charged to the former in 15.4 per cent., and to the latter in 9.6 per cent. The death rates for the two were 87.5 and 80 per cent., respectively. Hence, the occurrence of either of these organisms would appear to be of exceptionally grave prognostic significance. The tendency of *Streptococcus haemolyticus* to produce empyema has been clearly evident (four cases). Recent literature, however, has so repeatedly noted this fact that it is hardly necessary to stress its importance in this place.

I desire to place especial emphasis, however, on one fact developed in these studies for which I can find no figures to correspond in the literature. I refer to the large number of empyemas in these infants and children due to pneumococcus Type I. Of thirty-two cases of pneumonia charged to this type, 12 or 37.8 per cent. developed empyema. The incidence of empyema in the parallel series of Type I pneumonias in adults was 10.5 per cent. Of fifteen cases of postpneumonic empyema in children, admitted as such, eleven were caused by pneumococcus Type I. This organism has been responsible for 72 per cent. of the thirty-two cases of empyema which we have studied. In these infants and children there appears to have been almost as great a percentage liability to empyema from pneumococcus Type I, as from *Streptococcus haemolyticus*, while numerically the former has been much more important. If further studies establish that the application of these facts is permanent and general, not merely seasonal and local, data of considerable prognostic import will have been furnished for pneumonia in children.

Wherein lies the explanation of this exceptional liability to empyema in infections with Type I pneumococcus? It has already been suggested that the child appears, in general, to possess a natural immunity against pneumococcus superior to that of the average adult; witness the comparative mortality, type for type, in the parallel series of cases. On theoretical grounds, at least, it might be susceptible of argument that this liability to empyema is even an actual expression of such superior immunity. For in an individual susceptible to infection at all, the higher the degree of his immunity, natural or acquired, the more likely is the infection to be focal and not general. But the child's naturally superior immunity appears to extend to all types of pneumococcus, whereas it is only in infection with the one type that this extraordinary liability to empyema has been shown. Nor—and this is most important—is there any factor of artificial immunity to be reckoned with in these cases, for in none of them was serum administered. Of three children who received serum none developed empyema. In view of these facts, it seems more reasonable to explain this tendency to empyema with pneumococcus Type I, principally on the basis of some specific inherent property in the organism itself, or to some proper *modus operandi*. The smaller remaining factor will be some physical or anatomic factor in the child—this quite nonspecific—which renders him generally more subject to empyema than the adult.

These results have even a possible bearing on the treatment of Type I pneumonia in adults. There apparently exists in some quarters an opinion, however ill-grounded, that serum treatment predisposes to the development of empyema. The total independence of this phenomenon from specific therapy in these cases should go some way to

remove this superstition. Moreover, in six cases of Type I empyema following pneumonia in the adult series quoted, four developed in untreated cases. One wonders if even the reverse opinion may not be true—that the early and vigorous use of serum might not actually prevent this untoward development in many cases.

SUMMARY

1. Ninety-eight cases of lobar pneumonia, fifty-two cases of bronchopneumonia and fifteen cases of postpneumonic empyema have been studied bacteriologically in patients 12 years of age or younger.

2. In lobar pneumonia, or empyema following, pneumococcus Type I has been found in 29.9 per cent.; pneumococcus Type II (including atypical) in 3 per cent.; pneumococcus Type III in 7.1 per cent., and pneumococci of Group IV in 37.7 per cent. These figures represent a higher percentage of fixed types than the perusal of a rather meagre literature would have suggested.

3. The general reliability of these findings is suggested by the reasonably close correspondence to the findings in a parallel series of cases in adults. It is further suggested that the etiology of lobar pneumonia in infants and children follows in a general way that in adults for a given community at a given time.

4. Studies of comparative mortality suggest that the child possesses a better natural immunity against pneumococcus, type for type, than does the average adult.

5. In bronchopneumonia the fixed types of pneumococcus are much less common than in lobar pneumonia. Common mouth forms are relatively much more common. Regardless of type, the general mortality for bronchopneumonia is much greater than for lobar pneumonia. This is probably due to the conditions of origin and circumstances surrounding the former disease. *Streptococcus haemolyticus* and *Staphylococcus aureus* have been common in bronchopneumonia and have been followed by a particularly high mortality.

6. There has been an extraordinary tendency to the development of empyema in infections with pneumococcus Type I. Nearly 38 per cent. of pneumonias charged to this type developed this complication. Numerically it outranks any other cause of empyema in this series by about six times. This phenomenon bears no relation to the administration of serum.

It is hoped that further studies may be undertaken to determine the general applicability of these results.

CLINICAL DEPARTMENT

CONGENITAL TUBERCULOSIS WITH REPORT OF CASE *

GEORGE P. PRATT, B.Sc., M.D.

OMAHA

Pehu and Chaliér (1908, 1914 and 1915) from an extensive study of congenital tuberculosis accept only fifty-one cases as definitely proven. In the analysis of these cases they conclude that the father plays no part in the transmission, all the cases being the result of transplacental "heredocontagion." In all the cases admitted, the mothers had grave exacerbations of tuberculosis and they regard it as plausible that there was an acute generalization of the disease.

However, Weller (1916) and Warthin (1913) report cases of miliary tuberculosis of the placenta with latent tuberculosis in mothers, and Grulee and Harms (1915) report the case of a child succumbing on the eleventh day with generalized miliary tuberculosis whose mother had healed tuberculosis of the hip joint. Weber in a survey of congenital tuberculosis (1916) states: "It seems to me that we may well suppose that occasionally a mother with some form of chronic, and perhaps even latent tuberculosis, may suffer from a temporary condition of tuberculous 'bacilleemia' during pregnancy, without succumbing; for, probably conditions of temporary tuberculous 'bacilleemia' are not exceedingly rare in the subjects of chronic tuberculosis, apart from pregnancy."

These latter views are mentioned merely as possibilities and, perhaps, to arouse interest in this subject. The case which I am reporting conforms rigidly to the concepts of Pehu and Chaliér.

The condition in the foetus may be that of a true tuberculosis in which macroscopic and microscopic lesions are present or the status bacillaris described by J. Honl (1894) in which the tubercle bacilli can be found in the foetal organs, unaccompanied by macroscopic and microscopic changes.

REPORT OF CASE

CASE (No. 5290).—*History*.—A Mexican woman, married, aged 24, was admitted at the University Hospital, Jan. 6, 1921, in a critical condition, delirious, markedly cyanotic, breathing rapidly and perspiring freely. She complained

* Received for publication, Aug. 15, 1921.

* From the Medical Department of the University of Nebraska College of Medicine.

of pain in the chest, cough, headache and diarrhea. The first illness began one month ago with weakness, pain in the chest, cough, diarrhea and vomiting, the vomiting occurring after meals. The above symptoms gradually grew worse until two weeks prior to admission when she was confined to her bed. A physician called at this time, made a diagnosis of pneumonia. The symptoms have continued and increased since the onset.

Physical Examination.—The breasts were increased in size, pigmented and colostrum could readily be expressed from both nipples. The apex beat was located in the fifth interspace just inside the midclavicular line. No cardiac murmurs were heard and the second pulmonic sound was accentuated. The pulse was regular but weak. There was impaired resonance over the right base anteriorly and over both bases and apices posteriorly. Large and small bubbling râles and musical râles could be heard over the entire chest, both on inspiration and expiration. A slight friction was noted in the left post-axillary line. The abdominal wall on palpation was relaxed. The liver could be felt two fingers breadth below the costal margin and was slightly tender. The lower abdomen was filled with a palpable rounded mass extending to one inch below the umbilicus. A vaginal examination and the fetal heart tones confirmed a pregnant uterus.

The temperature dropped from 103 to 99 F. on the second day in the hospital and remitted then from 101 to 102 F. or 103 F. The respirations were always above 36 per minute, perhaps an average of 45. The pulse averaged between 115 and 130 until the end. The blood examination gave negative Widal reactions, negative blood cultures, a count of 5,600 leukocytes and a one plus Wassermann. At no time could tubercle bacilli be demonstrated in the scanty sputum. The urine was negative, except for a strongly positive diazo reaction.

Diagnosis.—The condition was diagnosed clinically as acute miliary tuberculosis and pregnancy. Death occurred Jan. 10, 1921.

Necropsy Report.—The necropsy revealed a generalized distribution of characteristic miliary tubercles in all the organs but most numerous in the lungs, making the case a predominant pulmonary form of miliary tuberculosis. The uterus was markedly enlarged, soft, congested and corresponded in size to that of five months pregnancy.

In order to facilitate the examination to determine the possibility of placental and fetal tuberculosis, the entire uterus with the fetus in situ was fixed in 20 per cent. liquor formaldehyd solution over night. The following morning the uterine cavity was opened and the fetus and placenta left exposed for forty-eight hours for complete fixation after which the abdominal cavity of the fetus was opened under aseptic precautions and free from contact with placenta or uterus. A distinct increase of straw-colored fluid was found in the fetal peritoneal cavity. Smears of this were negative for the bacillus of tuberculosis. No evidence of miliary tubercles was found in the abdominal cavity. The liver was somewhat enlarged and section was made of it in a dry field under aseptic precautions. Smears were made of scrapings from the cut surface and in these smears occasionally tubercle bacilli were found with Ziehl-Neelsen's carbolfuchsin stain. Similar smears were made from the placental cut surface before complete fixation, and prolonged search of these failed to reveal any tubercle bacilli.

The microscopic sections of the fetal liver, heart, lungs, spleen, kidney and intestines showed no tubercles and no thrombotic lesions. The microscopic sections of the placenta showed no tubercles and tubercle bacilli could not be demonstrated by stain and prolonged search.

Pathologic Diagnosis.—Miliary tuberculosis with predominant pulmonary localization; pregnancy; fetal tuberculosis without gross or microscopic lesions.

The finding of the tubercle bacilli in the fetal liver establishes this as a proven case of congenital tuberculosis which conforms to the status bacillaris of J. Honl, since no lesions of tuberculosis could be found after a careful microscopic examination of the fetal organs.

The most striking feature in the study is the difficulty of finding grossly or microscopically, pathologic evidence of tuberculosis or the tubercle bacillus in the placenta or fetus. It may be on account of this difficulty and because a thorough examination of placental tissue is not made routinely that we are lacking in the proof that tuberculosis may be congenitally transmitted from a mother with latent tuberculosis to children who develop the disease in the early months of life.

Thirty cents each will be paid for the following issues of the *AMERICAN JOURNAL OF DISEASES OF CHILDREN*: January, 1913; February, March, November and December, 1914; January and August, 1915; January, 1918; March and April, 1919. Address to *AMERICAN MEDICAL ASSOCIATION*, 535 North Dearborn Street, Chicago, Ill.

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IS THERE MORE THAN ONE KIND OF RICKETS?*

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For at least two years our attention has been attracted to the possibility of the existence of more than one kind of rickets. That is, under the head of rickets may be included more than one kind of disturbance of the mineral metabolism of the body which manifests itself in a characteristically defective growth and calcification of the bones. The possibility was suggested by a series of clinical observations concerning the association of rickets with other diseases or pathological conditions and certain peculiar manifestations of rickets itself in some children. Inasmuch, however, as the idea of the duality or multiplicity of rickets rested solely on clinical observations which, at most, were only of a suggestive nature, we have never felt justified in presenting it as a definite hypothesis. But, recently, our experiments with the rat have yielded results which strongly suggest that there may be two distinct forms of the disease.

EXPERIMENTAL EVIDENCE

In previous publications¹ we have described certain defective diets which, when fed to the young rat, produce marked disturbances in

* Received for publication Jan. 4, 1922.

¹ From the Laboratory of the Department of Chemical Hygiene, School of Hygiene and Public Health, the Johns Hopkins University.

1. Shipley, P. G.; Park, E. A.; McCollum, E. V., and Simmonds, Nina: Studies on Experimental Rickets. III. A Pathological Condition Bearing Fundamental Resemblances to Rickets of the Human Being Resulting from Diets Low in Phosphorus and Fat-Soluble A: The Phosphate ion in Its Prevention, Johns Hopkins Hosp. Bull. **32**:160 (May) 1921. McCollum, E. V.; Simmonds, Nina; Shipley, P. G., and Park, E. A.: VI. The Effects on Growing Rats of Diets Deficient in Calcium, Am. J. Hygiene **1**:492 (July) 1921. McCollum, E. V.; Simmonds, Nina; Shipley, P. G., and Park, E. A.: VIII. The Production of Rickets by Diets Low in Phosphorus and Fat-Soluble A, J. Biol. Chem. **47**:507 (Aug.) 1921. Shipley, P. G.; Park, E. A.; McCollum, E. V., and Simmonds, Nina: XVII. Am. J. Hygiene **2**: 1922.

the growth and calcification of the skeleton. The diets in question were alike in being insufficiently supplied with a factor or factors present in cod liver oil but differed from each other considerably in the composition of their mineral fraction, chiefly as regards the calcium and phosphorus. They may be divided into two groups according to the relative amounts of those two elements present. In one group the phosphorus was at a low level but the calcium at or above the level which would be optimal if all other dietary factors were satisfactory. In the other group the calcium was at an extremely low level but the phosphorus was not far from the optimal.

When the diets of the first group (those in which the phosphorus was deficient and the calcium phosphate ratio high) were fed to young rats living under ordinary laboratory conditions (room light), a pathologic condition of the skeleton developed, identical in all essential particulars with that seen in the rickets of human beings. The costochondral junctions were greatly enlarged; in some animals the thoracic wall was sunken at the sites of the costochondral junctions; the shafts of the ribs were fractured (Fig. 1). The long bones of the extremities were enlarged at the ends and could be cut easily. Between shaft and cartilage was a yellowish-white zone from two to three millimeters deep—the rachitic metaphysis. The proliferative cartilage extended in irregular prolongations toward the shaft. Calcium deposition in the cartilage was entirely lacking or extremely defective. The intermediate zone between cartilage and shaft was of a composition identical with that found in the metaphysis of the bones of rachitic children. It was composed of: cartilage in all stages of metaplasia or degeneration into a material indistinguishable from the osteoid; trabeculae consisting of osteoid; blood vessels; marrow elements; scattered, irregular deposits of calcified material encased in osteoid; and connective tissue. These were intermingled in a disorderly manner. The trabeculae of the shaft were surrounded by broad investments of osteoid (Figs. 2, 3 and 11).

When the diets of the second group (those in which the calcium was deficient, the phosphorus at a level not far from the optimal and the calcium-phosphate ratio low) were fed to rats kept under ordinary laboratory conditions (room light), a diseased condition of the skeleton developed which also bore marked resemblances to the lesions found in the rickets of human beings. The gross deformities caused by the second group of diets were as great or greater than those caused by the first group and corresponded exactly to the deformities found in rachitic children. The thorax was even more deformed than in the rats fed the diets of the first group; it was flattened from side to side and marked by deep grooves which followed the costochondral junc-

tions; the angular deformities produced at the junction of the costal cartilages and the shafts projected into its interior; the costochondral junctions were enlarged and greatly distorted; fractures in the shafts of the ribs were especially numerous (Fig. 4). The lower ends of radius and ulna were enlarged as were also the ends of all the long bones of the extremities and the bones were extremely soft and weak. Between the cartilage and the shaft was a white intermediate zone one to three millimeters deep. Microscopic examination showed that the cartilage was entirely or nearly free from calcium and was invaded in



Fig.1.—Pleural aspect of thorax of a rat which had developed rickets on diet 3,143 high in calcium and proportionately low in phosphorus.

an irregular manner by the vascular elements of the shaft. In consequence, the cartilage extended toward the shaft in irregular prolongations. The cells of the cartilage in proximity to the shaft showed evidences of degeneration and metaplasia. The intermediate zone was composed of cartilage in a more or less degenerated state, osteoid trabeculae, blood vessels surrounded by marrow elements, and a few deposits of calcium for the most part situated near the periphery and connective tissue. The trabeculae of the shaft were bordered by rather broad zones of osteoid. A loosely arranged fibrous tissue invested many of the trabeculae and in those places in which it filled in the

spaces between the trabeculae, it gave rise to histologic pictures which closely resembled those furnished by the fibrous marrow in the rickets of human beings (Figs. 5, 7, 8 and 10).

The pathologic condition induced in the bones by the diets of the second group did not, however, correspond at all points to that usually found in the human subjects of the disease. The metaphysis was composed in larger part of osteoid trabeculae. Though these osteoid trabeculae



Fig. 2.—Microphotograph of a bone showing low phosphorus rickets. Note the lack of calcification of the cartilage, the very wide metaphysis, and the osteoid tissue surrounding the calcified trabeculae of the shaft.

were free from calcium deposition, they nevertheless retained a certain semblance of orderly arrangement. The osteoid zones about the trabeculae were not always so broad as in the rats on the diets of the first group, though they were quite as broad as the osteoid borders in the bones of rachitic children (Figs. 6 and 7). Cells evidently

derived from the fixed tissues with large basophilic granulations were numerous in the immediate vicinity of the trabeculae (Fig. 9). Resorptive activity was exceedingly marked.

The abnormal condition of the skeleton produced by the faulty diets of the second group corresponded to that found in human beings with rickets in all fundamental respects, namely, the degenerative and metaplastic changes of the cartilage, the complete absence or defective character of the calcification of the cartilage, an abnormal amount of

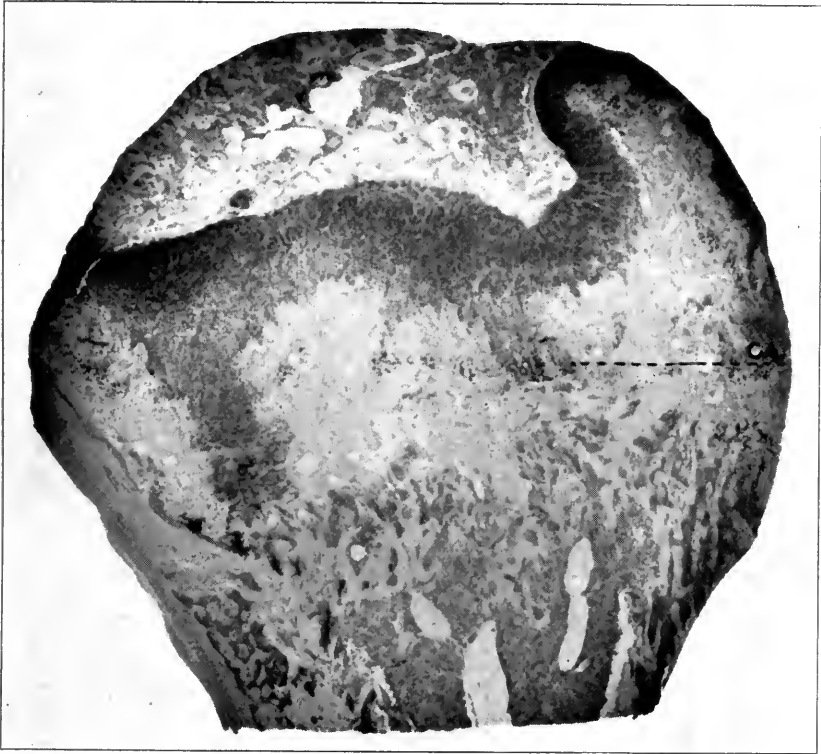


Fig. 3.—High calcium rickets in an animal on diet 3,133. This diet contains 2 per cent. added calcium carbonate instead of 3 per cent., as in diet 3,143. Note the linear deposit of calcium in the metaphysis, which marks an abortive attempt to heal.

osteoid production, irregular invasion of the cartilage, and the production of a rachitic intermediary zone. While one of the diets in question (diet 2638) did not give absolutely constant results in all animals, in some it produced a pathologic condition corresponding to that found in rickets of human beings even in its minor details.

DISCUSSION

Our experiments make it clear that, when the rat is deprived of certain active light rays and an unidentified factor contained in cod liver oil, a pathological condition corresponding in all fundamental respects to rickets in human beings can be produced through the diet in two ways: (1) by diminishing the phosphorus and supplying an optimal amount or an excess of calcium, or (2) by reducing the calcium and maintaining the phosphorus at a concentration somewhere near the optimum. In the first the calcium:phosphate ratio is large, in the second small. We are certain that in the human being similarly deprived of light and the unidentified factor it would also be possible to produce true rickets through a manipulation of the calcium and phosphate of the diet in the two ways mentioned.

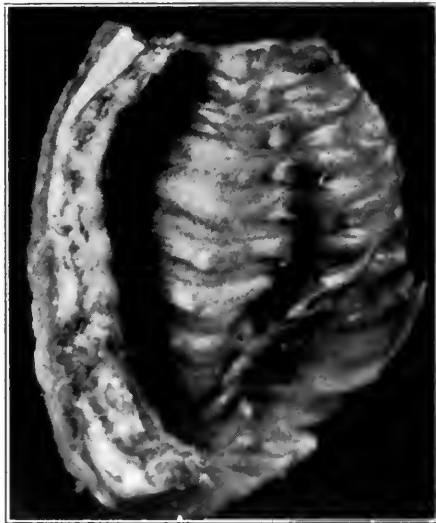


Fig. 4.—Pleural aspect of thorax of a rat which had developed low calcium rickets on diet 2,638, which is high in phosphorus relatively, and low in calcium.

As a result of our experiments we are led to believe that there are two main kinds of rickets. One is characterized by a normal or nearly normal blood calcium and a low blood phosphorus (low phosphorus rickets); the other by a normal or nearly normal blood phosphorus but a low blood calcium (low calcium rickets). The investigations of Howland and Kramer² and of Kramer, Tisdall and Howland³ on

2. Howland, J. and Kramer, B.: Calcium and Phosphorus in the Serum in Relation to Rickets, *Am. J. Dis. Child.* **22**:105 (Aug.) 1921.

3. Kramer, B.; Tisdall, F. F., and Howland, J.: Observations on Infantile Tetany, *Am. J. Dis. Child.* **22**:431 (Nov.) 1921.

the calcium and phosphorus content of the blood serum in rickets and tetany have given suggestive evidence in support of this idea. These observers found that in children suffering from rickets alone, the phosphorus of the blood serum is low, and the calcium not far removed from the normal; in children suffering from manifest tetany complicating rickets, on the other hand, the calcium is low but the phosphorus not far removed from normal.



Fig. 5.—Low power microphotograph showing low calcium rickets. The cartilage is extremely irregular, and many cells have undergone metaplasia into osteoid tissue. There are long tongues and islands of cartilage to be seen in the metaphysis, which contains almost no calcified bone. Magnification $\times 70$.

Rickets and Tetany.—As is well known, tetany complicates certain cases of rickets but not by any means all. Cases of rickets, even very severe rickets, exist in which tetany does not supervene, and, in all likelihood, never will. In other cases of rickets tetany either in the

manifest or in the latent form is present for weeks and numerous observers have pointed out that it is with the less severe forms of rickets that tetany usually allies itself. Furthermore, experience has shown that a cure in rickets accompanied by tetany is most easily accomplished through the administration of calcium and cod liver oil or calcium and heliotherapy, whereas in rickets uncomplicated with tetany the cure is most readily accomplished by means of the administration of cod liver oil or heliotherapy with or without phosphate. The

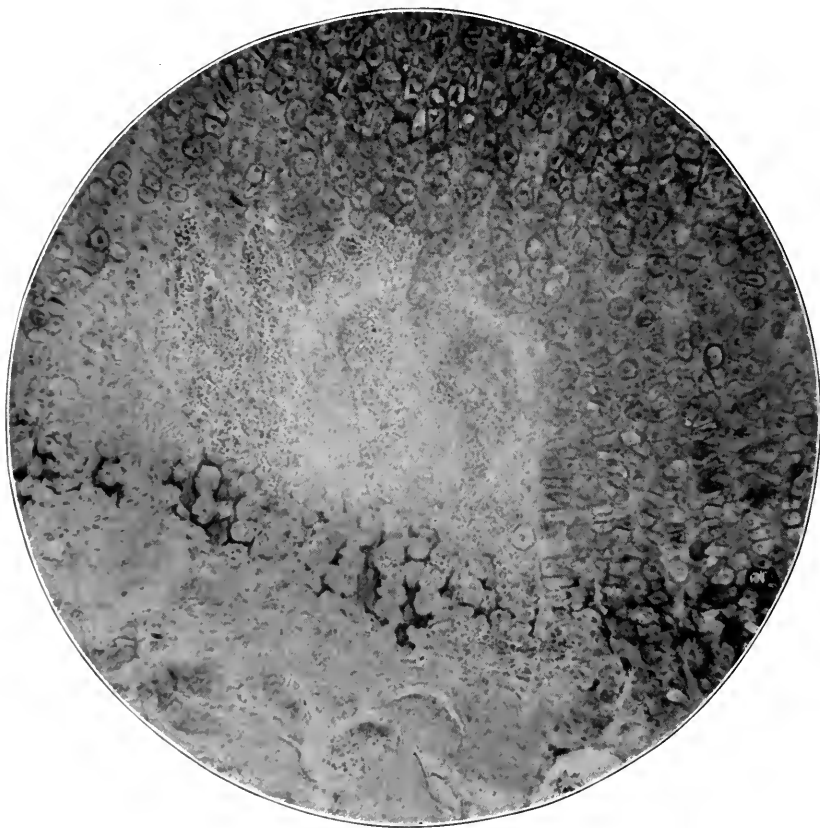


Fig. 6.—Microphotograph showing detail in the metaphysis of the bone (Fig. 3). Note the invasion of the cartilage by blood-vessels, its prolongation into the metaphysis, and the line of calcification (Ca) in the metaphysis which marks the occurrence of an aborted healing process.

chemistry of tetany, its occurrence in some cases of rickets but not in all, and the fact that the successful form of treatment differs with the presence or absence of tetany, rather strongly suggest that rickets with tetany and rickets without tetany are distinct forms of metabolic disturbance affecting the skeleton.

Recently Huldshinsky⁴ has advanced the view that tetany is nothing more or less than a symptom complex of healing rickets. While it is possible for tetany to occur with a healing rickets, clinical observation alone is enough to show that tetany does not ordinarily have that relationship to the disease. We have repeatedly seen children with rickets of the greatest severity undergo treatment with cod liver oil and have followed the healing process in the bones by means of the roentgen ray. None of the children ever showed the slightest evidence of tetany during the process of cure.



Fig. 7.—Low calcium rickets in the bone of an animal on diet 2,638.

It is undoubtedly true, however, that in some cases of rickets accompanied by tetany the roentgen ray shows deposition of lime salts at the cartilage-shaft junctions of the long bones of the extremities. The reason for this, according to the present trend of our investigations, is in many instances as follows: In the low calcium and the low phosphorus forms of rickets, calcium:phosphate ratios exist in

4. Huldshinsky, K.: Die Beeinflussung der Tetanie durch Ultraviolettlicht, *Ztschr. f. Kinderh.* **26**:5, 1920.

the blood which do not permit at all or permit only to a very limited extent the deposition of calcium phosphate in the bones. Between the low calcium form of the disease and the normal condition, on the one hand, and the low phosphorus form and the normal condition on the other, are innumerable gradations, presumably characterized by calcium:phosphate ratios in the blood, very probably oscillating ratios, which permit calcium phosphate deposition in varying degree, from the most



Fig. 8.—Low calcium rickets from a rat on diet 3,041. This diet contains the same amount of calcium as diet 2,638, but the phosphate content of the diet is slightly higher.

fragmentary to almost complete calcification (Figs. 3 and 6). In connection with both the low calcium and the low phosphorus forms of rickets, therefore, there are borderline states of the disease in which the calcium:phosphate ratios are such as to permit calcium phosphate deposition to take place irregularly or intermittently in the bones. With the borderline cases, in particular those connected with the low calcium form of the disease, we believe tetany to be frequently associated.

Our experiments indicate that deposits of calcium salts at the epiphyseal line may occur as a result of (1) healing in the low phosphorus form of rickets, (2) healing in the low calcium form and (3) as a constantly occurring or recurring phenomenon in the borderline states of the disease. With the first we believe that tetany is rarely associated and then, usually certainly, only in the latent form; with the second, tetany may be associated; with the third we believe it to be frequently associated.

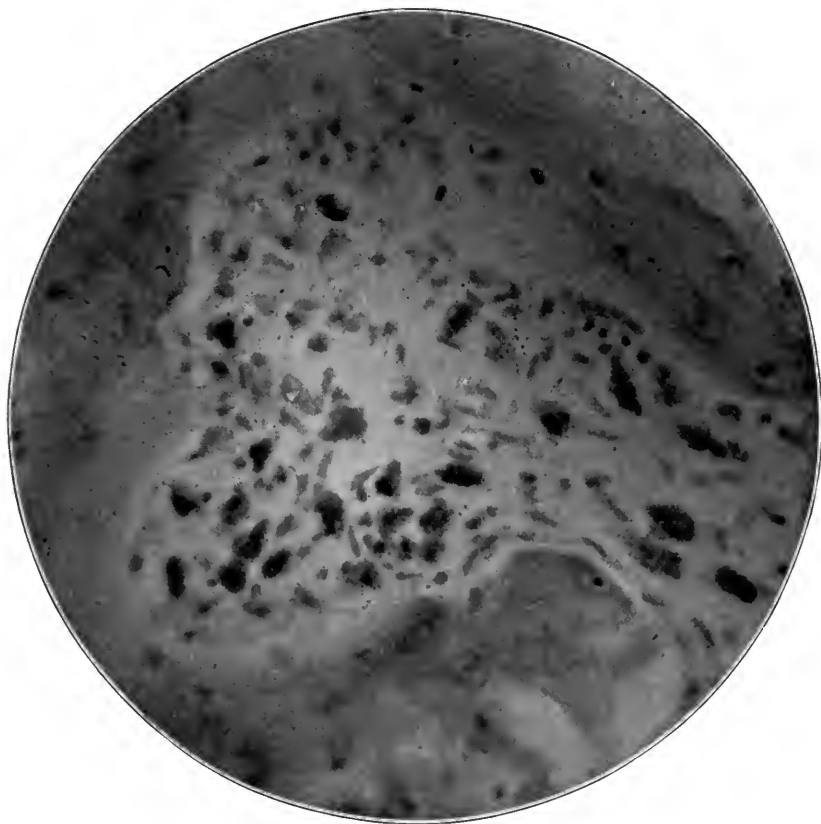


Fig. 9.—High power microphotograph showing basophil connective tissue cells near the trabeculae of bone in the shaft of an animal with low calcium rickets, diet 3,141.

According to present knowledge, the relationship between tetany and rickets appears to be as follows: Tetany is an expression on the part of the nervous tissues of an insufficiency of the calcium ion; rickets is an expression on the part of the skeleton of disturbed relations between the calcium and phosphate ions. The reason that tetany is so frequently associated with rickets is because rickets is a

disease in which the calcium ion in the body tissues and fluids is subject to wide variations. Tetany occurs independently of rickets, just as rickets occurs independently of tetany. Since tetany may occur with the low phosphorus form of rickets, it does not serve to mark off one form of rickets from the other. Tetany is essentially associated, however, with the low calcium form, and, for all practical purposes, the low calcium form of rickets is the rickets of tetany.

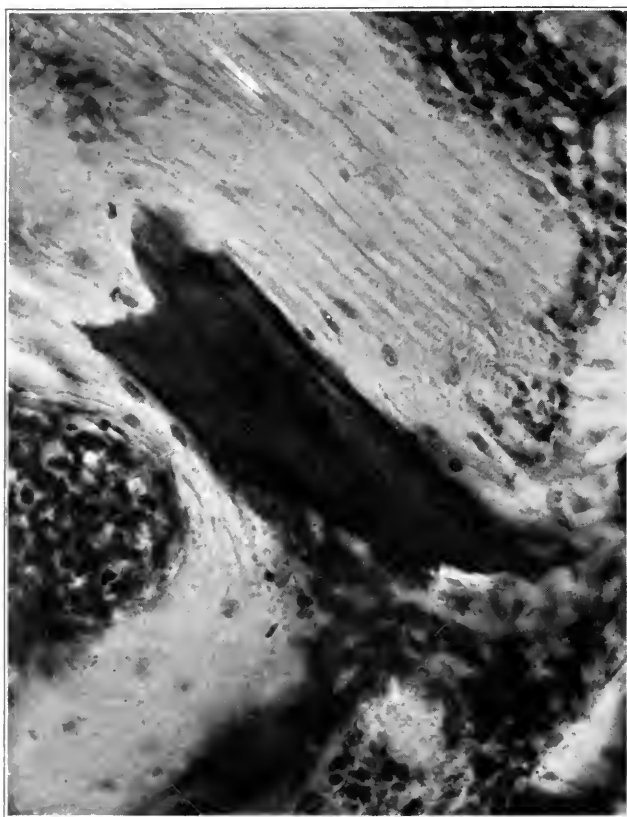


Fig. 10.—High power microphotograph to show the osteoid tissue from a case of low calcium rickets. Magnification $\times 375$.

Rickets and "Renal Dwarfism."—Recently Barber, Patterson and others have described children and young adults who were undersized, had rachitic deformities, and at the same time were the subjects of severe forms of chronic interstitial nephritis or developmental defects of the kidney. To the syndrome of symptoms which they exhibited, Barber gave the name "renal dwarfism." The age of one of Patterson's patients was only one year and 9 months, but all others were

between 6 and 20 years of age. If the infant described by Patterson be excepted, the height was from 6 to 16 inches under the average for the age, and the rickets was peculiar in that it was a late and gradual development (*rachitis tarda*). The disturbance of renal function in some of the cases was known to be extreme.

We have seen a child, aged 3½ years, whose case belongs in this category. The rachitic deformities were extreme. Moreover, the changes in the bones, as revealed by the roentgen ray and histologic examination, were most extensive and differed from the changes ordinarily found in rickets. The proliferative cartilage was most



Fig. 11.—This picture shows an osteoid and calcified bone in a trabecula from a case of low phosphorus rickets. Animal was on our diet 3,143. Same magnification as in Figure 10.

irregular and the calcification defective. In the deep metaphysis were large islands of cartilage bordered on one or more sides by dense calcium deposits. Those islands of cartilage gave to the metaphysis, as seen in the roentgenogram, a honeycomb appearance. The trabeculae were thin and the osteoid borders, comparatively speaking, narrow. Surrounding the trabeculae and islands of cartilage and lying between them was a loose fibrous tissue. Obviously, for a long time the pathologic condition in the bones had been in a state of flux between healing and relapse. The specific gravity of the urine was low and

appeared to be fixed. Albumen was constantly present. Several attacks which were thought to be uremic acidosis occurred. After death the kidneys were found to be exceedingly small and were defectively developed.

The histologic condition found in the bones of the infant described by Patterson appears to have been exactly similar.

It seems possible to us that the rickets which develops in the subjects of "renal dwarfism" has its origin in the extreme functional disability of the kidney and may belong to the low calcium form of the disease, i. e., that it may be dependent on an inability of the kidney properly to excrete phosphate. If our suggestion should prove to be correct, a true "renal rickets" exists and rickets under certain conditions may have an endogenous origin.

The Rickets Occurring in Children Suffering from the Severer Secondary Anemias.—Some infants develop a marked anemia which is apparently independent of concurrent infection. In many instances, it seems probable that this anemia is of dietetic origin, since breast feeding, or a diet almost entirely composed of cow's milk, has been unduly prolonged. The blood picture is that of a secondary anemia but sometimes corresponds to the picture generally known as von Jaksch's anemia. The children showing this abnormal condition of the blood regularly show rickets. The rachitic deformities are, however, somewhat different from those ordinarily seen and are fairly uniform. The frontal and parietal eminences are large and the regions of the sagittal and coronal sutures often appear sunken. The enlargement of the costochondral junctions and the ends of the long bones of the extremities is moderate and the degree of involvement at the cartilage-shaft junctions does not seem to be advanced. The involvement of the skull appears to be out of proportion to the involvement of the bones of the extremities or of the thorax.

We can form no definite idea concerning the nature of the disturbance in the metabolism which causes the rickets in the children suffering from severe secondary anemia. Probably the rickets and the anemia have a common origin, or are connected in some way. In any event it is interesting that in a recent series of experiments Happ⁵ was able to produce the most severe anemia and rickets in the rat by feeding certain diets extremely low in calcium. The experiments of Happ might indicate, therefore, that the rickets accompanying the severe so-called "alimentary" anemias belong to the low calcium form of the disease. Children showing the peculiar combination in question, however, failed to show evidences of tetany. It seems to us possible that the rickets accompanying the alimentary anemias may represent

5. Happ, W. M.: In press (Personal communication).

a somewhat different kind of disturbance in the mineral metabolism from the ordinary forms of the disease. Evidently another tissue, the blood, which is not regularly affected in rickets, is included in the metabolic disturbance.

We are prepared to find the etiology of rickets as varied as the etiology of tetany. Tetany was once considered to be an entity. Now, it is necessary to regard it as a symptom complex which can be produced experimentally in a variety of ways and which occurs naturally in several conditions. Tetany may be produced by excision of the parathyroid glands, by the injection into the blood stream of sodium phosphate or of sodium bicarbonate, by diets high in sodium phosphate and by the creation of gastric fistula which result in the loss of the gastric secretions. It occurs spontaneously in association with rickets and sometimes dilatation of the stomach. We should suppose that any influence which would result in the depression of the calcium or the phosphorus ions in the body fluids with the formation of the calcium:phosphate ratios favorable for the development of rickets if continued long enough would produce the disease and that there might be several such influences.

CONCLUSIONS

1. Our experiments make it clear that when the rat is deprived of certain active light rays and an unidentified factor contained in cod liver oil, a pathologic condition corresponding in all fundamental respects to rickets in human beings can be produced through the diet in two ways: (1) by diminishing the phosphorus and supplying the calcium in optimal quantities or in excess, or (2) by reducing the calcium and maintaining the phosphorus at a concentration somewhere near the optimum.

2. We believe it to be certain that in the human being, similarly deprived of light and the unidentified factor, it would also be possible to produce true rickets through an adjustment of the calcium and phosphorus of the diet in the two ways mentioned.

3. As the result of our experiments we are led to believe that there are two main kinds of rickets. One is characterized by a normal or nearly normal blood calcium and a low blood phosphorus (low phosphorus rickets); the other by a normal or nearly normal blood phosphorus but a low blood calcium (low calcium rickets).

4. If the hypothesis just stated is correct, the relation of tetany to rickets would appear to be as follows: Tetany is essentially an expression on the part of the nervous tissues of an insufficiency of the calcium ion; rickets is essentially an expression on the part of the skeleton of disturbed relations between the calcium and phosphate ions of the body fluids. Tetany is frequently associated with rickets

because rickets is a disease in which the calcium ion in the body tissues and fluids is subject to variations. Tetany occurs independently of rickets, just as rickets occurs independently of tetany. Since tetany may occur with the low phosphorus form of rickets, it does not serve to mark off one form of rickets from the other. Tetany, however, is essentially associated with the low calcium form of rickets, and, for all practical purposes, the low calcium form of rickets is the rickets of tetany.

5. It seems possible that the etiology of rickets may be as varied as the etiology of tetany. Our experiments lead us to suppose that in the absence of certain active light rays and an unidentified dietary factor contained in cod liver oil, any influence which would result in the depression of the calcium or phosphate ions in the body fluids with the formation of calcium:phosphate ratios favorable for the development of rickets would ultimately produce the disease. We are prepared to think that there may be several such influences.

6. For some time, as the result of clinical observations concerning curious associations of rickets with other pathologic conditions and certain peculiar manifestations of the disease in some children, our attention has been attracted to the possibility of the existence of more than one kind of rickets. In the light of our experiments we suggest the possibility that there may be a true renal rickets and that the rickets accompanying the alimentary anemias may represent a somewhat different kind of disturbance in metabolism from that which is present in the ordinary forms of the disease.

THE VALUE OF THE ROUTINE USE OF THE COLLOIDAL GOLD REACTION IN ACUTE EPIDEMIC POLIOMYELITIS*

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In 1916 Johnston¹ reported on the use of the colloidal gold test on the spinal fluid in four cases of poliomyelitis. He found an early transitory reaction in the syphilitic zone during the acute stage, and he considered that the test might prove an important aid in diagnosis. In March, 1917, Felton and Maxcy² published an excellent and important contribution on the subject. These investigators examined the spinal fluids of fifty-seven patients during various stages of the disease, and came to the following conclusions: (1) In the acute stage of poliomyelitis, the spinal fluid reacts with colloidal gold in dilutions of 1:40 to 1:60 producing a maximum decoloration of 3. (2) In the second and third weeks the reaction is practically the same, with a tendency to clear up in some cases and a precipitation in higher dilutions in others. (3) From the fourth to the eighth week, the curve runs practically parallel to the globulin and albumin content, persisting to the eighth week and beyond but still occurring in dilutions of from 1:40 to 1:60. (4) As the reaction is constantly in the same zone, the test is helpful in diagnosis.

Jeans and Johnston³ in the same month (March, 1917), reported the results of the examination of the cerebrospinal fluid in 100 cases of poliomyelitis in the acute stage. Fifty-five patients had definite paralysis and the fluids of the entire fifty-five gave a definite reduction of the gold chlorid solution in low dilutions of the spinal fluid. This reaction occurred with such uniformity that they believe the test is of distinct value in the diagnosis of poliomyelitis. In a few abortive cases and those in the preparalytic stage, the curve was not essentially different from that obtained in the clear cut paralysis cases. Jeans and Johnston emphasize the value of the test as a means of differential diagnosis from meningismus and other forms of meningitis.

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1. Johnston, M. R.: *Am. J. Dis. Child.* **12**:112 (Aug.) 1916.

2. Felton, L. D., and Maxcy, K. F.: *J. A. M. A.* **68**:752 (March 10) 1917.

3. Jeans, P. C., and Johnston, M. R.: *Am. J. Dis. Child.* **13**:239 (March) 1917.

Neal and Abramson⁴ in a detailed and careful study carried out during the 1916 epidemic on the spinal fluid in poliomyelitis, reported, among other tests, the results obtained with the colloidal gold reaction. They examined 114 cases, and found the result in seventy-seven of the fluids to fall in one of six curves as follows:

In 40 cases.....	1122100000	In 5 cases.....	1121100000
In 8 cases.....	1123210000	In 14 cases.....	1111000000
In 6 cases.....	1112210000	In 4 cases.....	1121000000

The remaining thirty-seven fluids gave various curves similar to the six foregoing but not exactly classifiable under any of the headings. The composite curve of the 114 spinal fluids was 1122100000. Neal and Abramson did not consider the gold chlorid reaction of absolute diagnostic value since they found that a few of the fluids from epidemic or tuberculous meningitis cases may also fall in these groups. They emphasize the fact that in only one instance was a poliomyelitis fluid negative, even in the case of fluids with normal chemistry, while the curves from cases of meningismus have been normal, even with a slightly increased chemistry, although not a sufficient number of fluids had been examined to be sure that this latter fact holds true in all cases.

Kolmer, Freese, Matsunami and Meuse,⁵ in a somewhat similar study of the spinal fluid from poliomyelitis cases, examined the fluids from thirty-eight cases by this reaction. The fluids from eighteen cases, removed from the second to the twelfth day after the onset of the paralysis, showed no color change at all; in four cases in the same stage there was only a slight precipitation in the first two tubes 1100000000—while all these fluids showed an increase in cells, and one of them in globulin. The fluids from ten cases, examined from two to twelve days after onset, yielded reactions of the syphilitic zone type with maximum precipitation in from 1:40 to 1:160, and decolorization usually terminating with blue. The fluids from six cases examined from twelve to nineteen days after the onset of paralysis yielded reactions of the meningitic zone type, characterized by maximum precipitation in from 1:80 to 1:320 to 1:640. In conclusion, Kolmer and his collaborators state that during the acute stage of poliomyelitis the fluid from 40 to 50 per cent. of the cases yielded a colloidal gold curve in the syphilitic and meningitic zone; a peculiar or definite curve of precipitation was not obtained by them.

Overholser⁶ applied the colloidal gold test to twenty-one specimens of spinal fluid from cases of poliomyelitis. Fourteen, or 66

4. Neal, J. B., and Abramson, H. L.: Arch. Int. Med. **19**:341 (Sept.) 1917.

5. Kolmer, J. A.; Freese, A. E.; Matsunami, T., and Meuse, B.: Am. J. Sc. **154**:720, 1917.

6. Overholser, W.: Boston M. & S. J. **177**:480 (Oct. 4) 1917.

per cent., gave a typical curve of the acute stage (112331000), the other curves were so anomalous that this investigator believed some technical error must be invoked to explain them. Larkin and Cornwall⁷ examined fifty spinal fluids by the colloidal gold test. In only two was a normal reaction obtained; 63 per cent. of the curves were humped, but they did not note any curve which was diagnostic of poliomyelitis. They found no parallelism to exist between the colloidal gold curve and the other spinal fluid or blood findings, but believed there was probably a tendency for the height of the curve to increase with the severity of the infection. Carr,⁸ in writing of the same series of cases, states that the reaction was in the syphilitic zone in 70 per cent. of the cases and that low curves were the rule. Vogel,⁹ in a general report of his work with this test, gives the result of its application in three cases of poliomyelitis; in one the curve was in the paretic zone and in two it was of a syphilitic type.

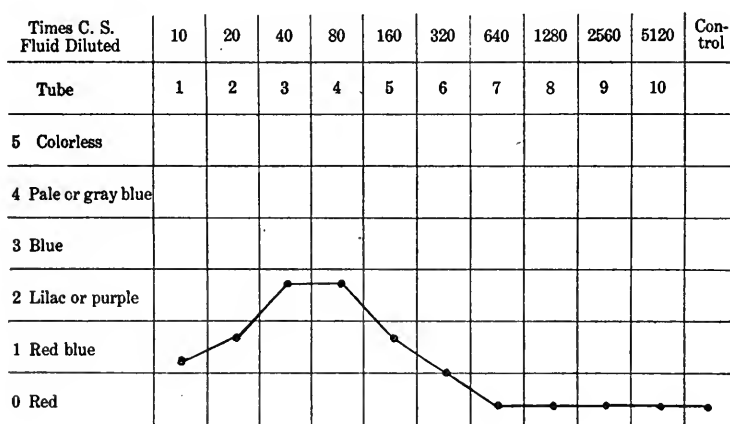


Fig. 1.—Average curve in first week of the disease.

During 1920, a small localized outbreak of poliomyelitis occurred in Brooklyn, and the Kingston Avenue Hospital admitted nineteen cases from August 24 to November 26. Subsequently two additional cases were received, making a total of twenty-one. In this series there were four fatalities, due to poliomyelitis, the four patients entering the hospital on or about the same date (November 11). The predominant type of the disease was that usually seen, the spinal or myelitic, with, however, an unusually high percentage of cases with moderate or marked polyneuritic symptoms, which in a few instances made up the most pronounced features of the malady.

7. Larkin, J. H., and Cornwall, L. H.: *Arch. Pediat.* **35**:459, 1918.

8. Carr, W. L.: *Arch. Pediat.* **34**:591 (Aug.) 1917.

9. Vogel, K. M.: *Arch. Int. Med.* **21**:496 (Oct.) 1918.

The colloidal gold reaction was performed in each of the twenty-one cases included in our series, and a total of seventy-four spinal fluids from these twenty-one patients were examined in various stages of the disease from the fourth to the one hundred and twenty-third day. Classified according to the week in which they were taken, the fluids were divided as follows:

First week.....	6 fluids	Eighth week.....	5 fluids
Second week.....	11 fluids	Ninth week.....	5 fluids
Third week.....	11 fluids	Tenth week.....	4 fluids
Fourth week.....	7 fluids	Eleventh week.....	3 fluids
Fifth week.....	6 fluids	Fourteenth week.....	1 fluid
Sixth week.....	10 fluids	Eighteenth week.....	1 fluid
Seventh week.....	4 fluids	Total	74 fluids

Results Obtained.—In this series, in no instance was the colloidal gold reaction normal when the spinal fluid was examined during the first three weeks of the disease. The curve obtained was constantly in the same zone.

In order to show the characteristics of the curve in poliomyelitis, we have separated our results according to the weeks of the disease in which they were obtained, and have on this basis separately constructed an average curve for each week up to the eighth. The curves for the first, second, fourth, sixth and eighth weeks are shown in Figures 1, 2, 3 and 4. These figures show the average characteristics of the reaction obtained at various periods of the disease in this series. It is noticeable that the curve for the first two weeks is very much the same, and is what we believe may be considered characteristic of this stage. In the first week it consists of an ascending curve presenting a gradual increase in reduction in higher dilutions starting in the reddish blue color in 1:10, extending into the lilac or purple color in 1:40 and 1:80, and then descending also gradually but more abruptly into the reddish blue again in 1:160 and reaching the nonreducing or red area in 1:640. In the second week, it differs only in that it remains in the lilac or purple area from 1:40 to 1:160.

As the disease progresses the average curve gradually falls, reaching normal in a minor proportion of the cases from the eighth to the ninth week of the malady. Thus, out of a total of ten fluids taken up to or beyond the ninth week, three showed a normal reaction before this period. One of these appeared on the twenty-eighth day, another on the fifty-third day, and a third on the fifty-fifth day. Of the seven fluids which remained elevated beyond the ninth week, three continued showing an acute poliomyelitis curve until the eleventh week, and one until the fourteenth week, to be exact, the one hundred and twenty-third day. In this series, therefore, 30 per cent. of the cases of poliomyelitis presented a normal reduction of colloidal gold at the end of the

ninth week. How long the curve remained elevated in the remaining 70 per cent. of the cases we were unable to determine, owing to the discharge of the patients from the hospital. We are cognizant of one case which is suggestive of the possible duration of a positive reaction in exceptionally severe attacks:

A young girl, 15 years of age, was admitted to the Kingston Avenue Hospital during the epidemic of 1916, with a very extensive paralysis involving the muscles of all the extremities, back and neck. After her discharge from the hospital, the patient had what she terms three relapses; in the first she was confined to bed two months, in the second for two years, and in the third for one year. She was admitted to the Kings County Hospital in 1920, suffering from chorea and residual paralysis of her left leg, back and some of the muscles of her neck. Two spinal fluids taken after admission showed a negative Wassermann, slight increase in cells and globulin, and a colloidal gold curve of 1122100000.

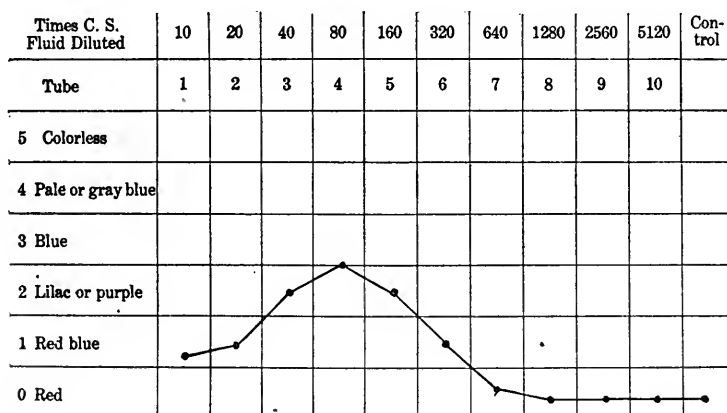


Fig. 2.—Average curve in second week of the disease.

This case is cited as an example of the possibility of a long persistence of colloidal gold reaction in a patient with severe infection. Of course, it cannot be absolutely proven that the curve was due to poliomyelitis, but the case is suggestive.

A very early subsidence of the curve, such as the twenty-eighth day (Case 1987) is exceptional. It occurred in a patient with moderate paralysis and slight polyneuritic involvement, who made a rapid recovery. On the other hand, patients with a persistence of a positive reaction of an acute type beyond the ninth week have usually presented a marked and extensive paralysis (Cases 1840, 1895 and 1990) with moderate or marked and persistent polyneuritis, or a mild paralysis with persistent and marked polyneuritis (Case 1011). It seems to us from this somewhat limited study, that there is a definite relationship between the duration of the positive colloidal gold reaction

and the persistence of polyneuritic symptoms and to a lesser extent paralysis. Patients who run an acute curve late in the disease usually present also some degree of persistence of the acute hydrocephalus which occur during the early weeks of the malady, and the fluid obtained on lumbar puncture continues to be increased in amount and in pressure. We are strongly inclined to believe that the period when the colloidal gold reaction returns to the normal indicates, as a rule, the end of the acute stage of the disease, and is, therefore, of great value in that one may determine more concisely than is done at present when the prolonged rest of the acute stage may be terminated, and the more active measures of treatment of the residual paralysis may be undertaken by massage, electricity, etc. The reaction seems to indicate better than any other means, such as the study of cytology and chemistry of the spinal fluid, or of the symptoms, when the acute generalized inflammation of the meninges, cord and brain has approximately subsided. It seems probable that all active methods of treatment for the subsequent paralysis are strongly contraindicated until this stage is passed. There is also another aspect, and that is that the extent of the paralysis which may remain and require treatment can best be judged when the reaction becomes normal, for throughout the period of its elevation great spontaneous improvement usually continues to occur.

In three of the seven cases presenting a curve beyond the ninth week, the reaction had begun to descend in the third or fourth week, but was subsequently found more elevated in the ninth, tenth or eleventh weeks. The average curve obtained, however, gradually falls as the disease advances. In the first and second weeks (Figs. 1 and 2) there is little variation. In the third week the average curve reaches high into the lilac area in 1:80 and the ascending line is definitely beginning to decline. In the fourth week (Fig. 3) there is a marked change in the curve consisting of a pronounced flattening out, and it is limited to the red blue area, from 1:10 to 1:320. From the fifth week to the ninth week (Fig. 4), the curve gradually continues to subside, the slight reduction obtained in the red blue color being gradually more and more limited to the lower dilutions.

There was only an inconstant relationship between the cytologic and chemical findings of the spinal fluid and the colloidal gold curve in this series. As a rule, as the reaction subsided, the globulin diminished, but, on the other hand, many cases presented a high curve late in the disease with a normal or almost normal globulin reduction. We did not note that in the first few weeks of the disease the augmentation of globulin and cells bore any relation to the height of the gold chlorid curve.

The average curve (Fig. 5) in the fatal cases is very similar to that obtained in the first and second weeks of the disease in the more severe nonfatal cases. Although in fatal cases it may tend to exhibit slightly greater precipitation and to be on the average a higher curve, there has not been sufficient difference in our series to make the test of any definite value from the prognostic viewpoint.

It is conceded by most workers who have studied the spinal fluid in cases of epidemic poliomyelitis, that there is nothing about the findings which is entirely characteristic of that disease. Thus, an increase in cells, lymphocytes or of globulin and a good (3+) reduction of Fehling's solution is merely confirmatory in a case in which the clinical diagnosis is clearly established. On the other hand, many

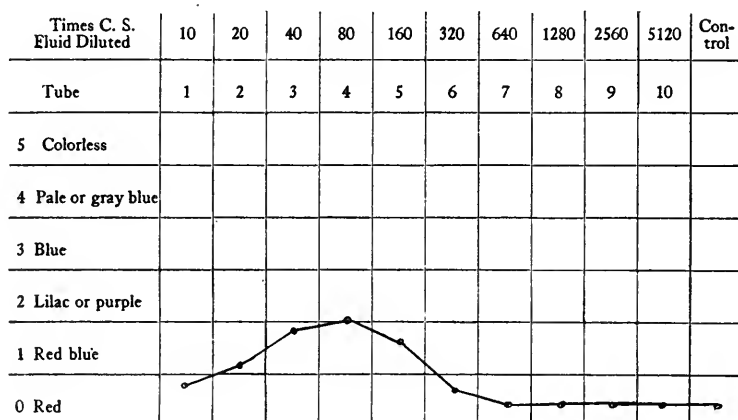


Fig. 3.—Average curve in fourth week of the disease.

cases of poliomyelitis do not present, when they come under observation any increase in cells, or if so, it is little above normal and the globulin may not be augmented. While in other conditions, such as meningismus or tuberculous meningitis, there may be an increase in globulin, as in the former, or an increase in globulin and cells, as in the latter. Hence, positive or negative findings in the spinal fluid as regards cytology or chemistry cannot be considered in the least conclusive. Especially is this the case if poliomyelitis is sporadic and the type atypical, presenting itself in one of its less common forms, such as the meningitic, encephalitic, ataxic, polyneuritic or abortive varieties, or in those cases in which it occurs as a Landry's paralysis, or in which a facial palsy may be the only paralytic involvement present. In such circumstances we need a finer laboratory test to establish the diagnosis, and we believe this is fulfilled by the gold chlorid reaction.

ANALYSIS OF CASES AS TO PRESENCE OF PARALYSIS ON ADMISSION AND ON DISCHARGE, AND DEGREE OF COLLOIDAL GOLD REACTION

Case No.	Date Admitted to Hospital	Days in Admission	Type of Disease	Paralysis on Admission	Degree of Polyn. neuritis	Dates of Spinal Fluid Examination	Colloidal Gold Reaction										Paralysis on Discharge	Polyneuritis on Discharge	Degree of Improvement	Recovered or Died
1900	9/26	20	Myelitic, polynucleitic, bulbar	Left arm, complete; legs, complete; back, complete; cranial nerves, involved	2+	10/5 10/15 10/29 11/5 11/17 12/8 1/5	1 2 1 1 0 0 0 0 0 1 1 1/2 1 0 0 0 0 0 1 1 2 0 0 0 0 0 0 0 1 2 2 0 0 0 0 0 1 2 1 0 0 0 0 0 0 1 2 2 1 1 0 0 0 0 2 3 2 1 0 0 0 0 0	0 0 0 0 0 0 0	Right leg, complete; left leg, partial; back, complete; cranial nerves, involved	1+	Slight	Recovered								
561	2/18	4	Myelitic, polynucleitic	Legs and neck, complete...	3+	3/1 4/18	1 1 2 3 2 1 1 0 0 1 1 2 2 0 0 0 0 0	0 0	Right leg, complete; left leg, partial; back, complete	2+	Slight	Recovered								
1991	9/29	8	Myelitic	Right leg, partial.....	—	10/7 10/14 10/28 11/4 11/11	0 0 1 2 0 0 0 0 0 0 0 1 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0	0 0 0 0 0	None.....	—	Moderate	Recovered								
2196	11/6	12	Myelitic, polynucleitic, bulbar	Legs, complete; diaphragm, weak; back, complete; cranial nerves, involved	3+	12/2	1 1/2 2 1 0 0 0 0 0	0	Legs and back, complete; cranial nerves, involved	2+	Slight	Recovered								
2005	10/2	6	Myelitic	Legs, partial.....	—	10/15 10/30 11/5 11/15	1 1 2 2 1 1 0 0 0 1 1 2 1 0 0 0 0 0 0 1 1/2 1 0 0 0 0 0 1 1 2 1 1 0 0 0 0	0 0 0 0	Legs, weak.....	—	Moderate	Recovered								
2130	10/24	2	Meningitic	None.....	—	10/25 11/8 11/23	1 2 2 1/2 0 0 0 0 0 0 1 2 2 1/2 1 0 0 0 0 0 1/2 0 1/2 2 1 0 0 0 0	0 0 0	None.....	—	Marked	Recovered								
1987	9/28	4	Myelitic, polynucleitic	Legs and back, complete...	2+	9/30 10/21 10/28 11/4	0 0 2 3 2 0	0 0 0 0	Right leg, partial.....	—	Marked	Recovered								
1929	9/16	4	Myelitic, polynucleitic	Right arm, weak; legs, weak; back, weak	2+	9/22 10/3 10/14 10/29 11/11 11/22	1 1 2 2 1/2 2 1 0 0 0 1/2 1/2 2 1 0 0 0 0 0 0 1 2 1 0 0 0 0 0 1/2 1/2 1 0 0 0 0 0 1 1 1/2 3 3 2 0 0 0 1 1 2 2 1/2 1 0 0 0	0 0 0 0 0 0	None.....	2+	Marked	Recovered								
1011	10/4	9	Myelitic, polynucleitic, meningitic	Legs, partial.....	3+	10/6 10/12 10/21 11/4 11/11 11/21	0 1/2 2 3 2 2 1 0 0 0 1/2 0 1/2 2 2 0 0 0 0 1/2 1 2 2 0 0 0 0 0 1 1 2 2 1/2 1 0 0 1 2 2 3 0 0 0 0 0 1 1 1 1/2 1/2 1 1 0 0	0 0 0 0 0 0	Left leg, partial.....	2+	Marked	Recovered								

2266	11/18	2	Meningitic,	2+	11/24 12/ 2 12/ 8	0 0 1 2 2 1 0 0 0 0 0 1/2 2 2 1 0 0 0 0 0 0 1 2 2 1 1/2 0 0 0 0	0 0 1 2 2 1 0 0 0 0 0 1/2 2 2 1 1/2 0 0 0 0 0 1 2 2 3 2 1 0 0 0	0 0 1 2 2 1 0 0 0 0 0 1/2 2 2 1 1/2 0 0 0 0 0 1 2 2 3 2 1 0 0 0	Legs, weak.....	2+	Moderate	Recovered
1895	9/ 6	4	Myelitic, meningitic, polynuritic	Right arm and legs, partial; back and neck, weak; cranial nerves, involved	2+	9/20 11/ 5 11/ 8	1 2 2 3 2 1 0 0 0 0 1 1/2 3 2 2 1 0 0 0 0 1 2 2 2 2 1 0 0 0 0	1 2 2 3 2 1 0 0 0 0 1 1/2 3 2 2 1 0 0 0 0 1 2 2 2 2 1 0 0 0 0	1 2 2 3 2 1 0 0 0 0 1 1/2 3 2 2 1 0 0 0 0 1 2 2 2 2 1 0 0 0 0	Right arm, weak; right leg, partial; cranial nerves, involved	Moderate	Moderate	Recovered
2113	10/21	3	Myelitic, polynuritic	Right leg, partial.....	2+	11/ 2 11/24	0 1/2 0 1/2 2 2 1 1/2 0 0 0 1 2 2 2 3 2 0 0 0 0	0 1/2 0 1/2 2 2 1 1/2 0 0 0 1 2 2 2 3 2 0 0 0 0	0 1/2 0 1/2 2 2 1 1/2 0 0 0 1 2 2 2 3 2 0 0 0 0	Left leg, weak.....	None	Moderate	Recovered
2019	10/ 5	7	Myelitic	Right leg, partial.....	2+	10/ 6 10/14 10/28 11/ 8 11/12 11/21	0 1/2 1 2 2 1 0 0 0 0 0 0 0 1/2 1 0 0 0 0 0 0 0 0 1/2 1 0 0 0 0 0 0 1 2 2 1 1 0 0 0 0 1 2 2 2 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	0 1/2 1 2 2 1 0 0 0 0 0 0 0 1/2 1 0 0 0 0 0 0 0 0 1/2 1 0 0 0 0 0 0 1 2 2 1 1 0 0 0 0 1 2 2 2 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	0 1/2 1 2 2 1 0 0 0 0 0 0 0 1/2 1 0 0 0 0 0 0 0 0 1/2 1 0 0 0 0 0 0 1 2 2 1 1 0 0 0 0 1 2 2 2 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	None.....	None	Marked	Recovered
2320	11/26	7	Myelitic, polynuritic	Legs, complete; back and neck, weak	3+	11/27 12/ 4 1/ 5	0 1/2 1 1/2 2 1 0 0 0 0 1 1/2 1/2 3 3 2 0 0 0 0 0 2 2 1 0 0 0 0 0	0 1/2 1 1/2 2 1 0 0 0 0 1 1/2 1/2 3 3 2 0 0 0 0 0 2 2 1 0 0 0 0 0	0 1/2 1 1/2 2 1 0 0 0 0 1 1/2 1/2 3 3 2 0 0 0 0 0 2 2 1 0 0 0 0 0	Right leg, weak; left leg, partial	None	Moderate	Recovered
1840	8/24	4	Myelitic, polynuritic, bulbar	Arms and legs, complete; diaphragm and intercostals, weak; back and neck, complete; cranial nerves, involved	3+	10/21 10/28 11/ 5	0 1 1 3 1 0 0 0 0 0 0 0 1/2 2 1/2 1 0 0 0 0 1 2 2 2 1 0 0 0 0 0	0 1 1 3 1 0 0 0 0 0 0 0 1/2 2 1/2 1 0 0 0 0 1 2 2 2 1 0 0 0 0 0	0 1 1 3 1 0 0 0 0 0 0 0 1/2 2 1/2 1 0 0 0 0 1 2 2 2 1 0 0 0 0 0	Arms, partial; legs, complete; back and neck, complete; diaphragm and intercostals, weak; cranial nerves, complete	Moderate	Slight	Recovered
2035	10/ 7	8	Myelitic, polynuritic	Legs, weak; back and neck, weak	3+	10/28	0 1 2 2 2 1 0 0 0 0	0 1 2 2 2 1 0 0 0 0	0 1 2 2 2 1 0 0 0 0	Moderate	Recovered of polymyelitis
2044	10/ 9	5	Myelitic, bulbar	Arms and legs, complete; diaphragm and intercostals, weak; back and neck, complete	1+	10/12 10/21 11/11 11/24 12/ 2	1 1 2 3 3 1 0 0 0 0 1 1 2 3 3 1 0 0 0 0 2 3 3 3 1 0 0 0 0 0 1 2 3 2 1 0 0 0 0 0 0 1/2 1 1/2 1 1/2 1 0 0 0 0	1 1 2 3 3 1 0 0 0 0 1 1 2 3 3 1 0 0 0 0 2 3 3 3 1 0 0 0 0 0 1 2 3 2 1 0 0 0 0 0 0 1/2 1 1/2 1 1/2 1 0 0 0 0	1 1 2 3 3 1 0 0 0 0 1 1 2 3 3 1 0 0 0 0 2 3 3 3 1 0 0 0 0 0 1 2 3 2 1 0 0 0 0 0 0 1/2 1 1/2 1 1/2 1 0 0 0 0	Arms, partial; legs, partial; back and neck weak	Moderate	Moderate	Recovered
2273	11/19	2	Myelitic, polynuritic, bulbar	Left leg, diaphragm, intercostals and neck, partial; cranial nerves, involved	1+	11/20	0 0 1 2 1/2 1 0 0 0 0	0 0 1 2 1/2 1 0 0 0 0	0 0 1 2 1/2 1 0 0 0 0	Died, 11/21
2229	11/11	4	Ascending Landry's	Left arm and legs, complete; diaphragm and intercostals, partial; neck and back, weak; cranial nerves, involved	-	11/12 11/16 11/17	1 2 1/2 2 2 1 0 0 0 0 1 1/2 3 2 1 0 0 0 0 0 1 1 1 2 3 2 0 0 0 0	1 2 1/2 2 2 1 0 0 0 0 1 1/2 3 2 1 0 0 0 0 0 1 1 1 2 3 2 0 0 0 0	1 2 1/2 2 2 1 0 0 0 0 1 1/2 3 2 1 0 0 0 0 0 1 1 1 2 3 2 0 0 0 0	Died, 11/19
2226	11/11	4	Myelitic, bulbar	Left arm and legs, complete; diaphragm and intercostals, partial; neck and back, partial; cranial nerves, complete	1+	11/13 11/18	1 1 2 1 0 0 0 0 0 0 1 1 2 3 3 1 0 0 0 0	1 1 2 1 0 0 0 0 0 0 1 1 2 3 3 1 0 0 0 0	1 1 2 1 0 0 0 0 0 0 1 1 2 3 3 1 0 0 0 0	Died, 11/18
2230	11/11	2	Myelitic, meningitic, bulbar	Arms and legs, complete; diaphragm and intercostals, partial; neck, complete	1+	11/12	1 2 3 3 2 1 0 0 0 0	1 2 3 3 2 1 0 0 0 0	1 2 3 3 2 1 0 0 0 0	Died, 11/13

In order to show the differential value of the curve obtained in the early weeks of the disease, we have placed in Figure 6 all reactions found during the first ten days or in what might be termed the very acute febrile stage. This, then, forms by its limitations what might be termed for descriptive purposes a poliomyelitic zone. It has been cross sectioned and is thus represented in the figure, and for comparison we have included the curves of various other well recognized meningeal conditions. The figure shows clearly that the zone of Heine-Medin's disease, as made out in this small series, is not identical with that of any other disease.

It is true; that a number of curves are obtained in cases of cerebrospinal syphilis which run a low course, and in which there may be a close resemblance to a poliomyelitic reduction. But while such cases occur not infrequently, the clinical history and symptoms of the two diseases are so different that confusion is entirely improbable. The Wassermann test is moreover, available.

A typical curve of tuberculous meningitis would not be confused with any of our poliomyelitis curves. We have purposely selected as an example of a tuberculous meningitis curve for Figure 6 one which is of as mild a type as was obtainable and one which resembled as much as any which are ordinarily encountered the curve of Heine-Medin's disease. Yet even here the distinction is definite and clear cut, so far as the acute febrile stage of poliomyelitis is concerned. In tuberculous meningitis the curve begins to rise in higher dilutions, not lower commonly than 1:40, and is prolonged well into the meningeal zone in the vast majority of instances, rarely falling below the lilac purple in a dilution less than 1:640.

It must be stated, however, that occasionally one encounters cases, usually those with either marked polyneuritic or meningitic symptoms, in which the gold chlorid curve toward the end of the second week is prolonged slightly beyond the limits of the poliomyelitis zone (Cases 1929 and 1011). Obviously at this period of the disease the question of a differential diagnosis from tuberculous meningitis would not arise.

It must always be kept in mind that if a curve is obtained which transgresses definitely on the meningeal zone, tuberculous meningitis should be ruled out carefully, as the results of our work and that of the majority of our predecessors seem to show that such a reaction is altogether exceptional in the very acute stage of epidemic poliomyelitis.

The colloidal gold reaction is rarely required in the differential diagnosis of poliomyelitis and epidemic cerebrospinal meningitis or any other form of purulent meningitis owing to the entirely different macroscopic, cytologic and chemical characteristics of the spinal fluids in the two diseases. It is possible that in early cases the test might have to be invoked in so much as that in the preparalytic stage of

Heine Medin's disease the cell count is sometimes so augmented as to give a faint hazy appearance to the fluid, while, on the other hand, in the very early stage of epidemic meningitis the fluid may be almost clear, or have a faint opalescence. From Figure 6 it is evident how distinctly different the curves are in the two maladies

As previous work has shown, Lange's colloidal gold test provides the only certain method of differentiating poliomyelitis, and the various forms of meningismus. It was not uncommon during the 1916 epidemic to see cases in which a diagnosis of Heine-Medin's disease had been made in cases which were not such. Thus, occasionally, cases of scurvy, rickets, tetany, etc. were so diagnosed, and, still more commonly, cases of meningismus complicating diverse conditions such as bronchopneumonia, gastro-enteritis or colitis were confused with poliomyelitis. A negative spinal fluid did not absolutely exclude

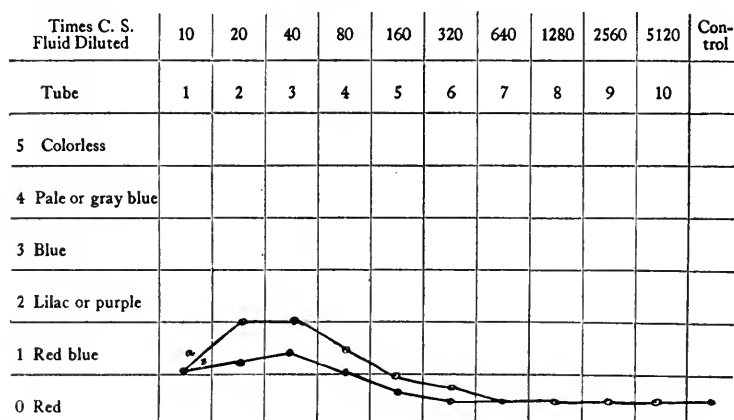


Fig. 4.—Average curve in sixth (a) and eighth (b) week of the disease.

poliomyelitis, while a positive fluid, as regards chemistry, did not prove it to be the latter. Had the colloidal gold chlorid test been employed as a routine in such instances there is no doubt the diagnosis would have been determined more accurately and more quickly. We have employed the test in this way in several cases during the past year, and in no instance did we obtain a reduction of colloidal gold in meningismus. In one case of scarlet fever and poliomyelitis (Case 2266), the diagnosis on admission was meningismus complicating scarlet fever, and we should not have recognized the fact that a mixed infection with the two diseases existed until a later period, after paralysis was definitely manifest, if it had not been for this test. In another patient (Case 24), in whom the physical signs of pneumonia were late in appearing, but who presented a pronounced meningeal syndrome including spastic paralysis of the left arm and leg, due to a lesion in the

course of the upper motor neuron, we were able to rule out Heine-Medin's disease in this way.

As to the value of the colloidal gold test in differentiating poliomyelitis and epidemic encephalitis, the literature gives no information. There has been relatively little work carried out on the use of this test in epidemic encephalitis. Among the few reports made on the subject are those of Tilney and Howe,¹⁰ Davis and Kraus,¹¹ and Nixon and Sweetser.¹²

Tilney and Howe state that in the greater proportion of cases reported the spinal fluid has been normal and that the colloidal gold curve in the few cases in which it has been studied has been negative. In their case reports are included five cases in which colloidal gold reactions were performed. In three instances the test was negative, and in the remaining two the findings were 1223432100 and 11½22 11½00000.

David and Kraus reported thirty-four cases of epidemic encephalitis, in which forty-three examinations of the spinal fluid were made with the colloidal gold test. Nineteen were in the first three weeks of the disease. Fourteen spinal fluids were absolutely negative; in the remaining five cases the results were as follows: 1112100000; 0000110000; 0001210000; 0012231000; 1122100000. Of the fluids twenty-four taken in the later weeks of the disease, from the fourth to the sixteenth, negative results were obtained in ten, the remaining positive reactions being extremely variable.

Nixon and Sweetser, in an examination of ten spinal fluids obtained from five patients with encephalitis, found the colloidal gold curves exceedingly variable, as follows:

1 2 2 1 1 1 2 0 0	5 5 4 3 3 3 3 2 0
0 0 0 1 1 2 1 0 0	1 1 3 3 3 2 1 0 0
0 0 1 1 1 0 0 0 0	1 1 3 4 4 3 2 1 0
0 0 1 1 1 0 0 0 0	0 1 1 3 3 3 2 1 0
1 2 2 4 4 4 3 3 0	0 0 1 1 2 0 0 1 0

One of us has had five cases of epidemic encephalitis come under his observation and the curves in these cases were as follows:

0 1 1 1 1 0 0 0 0 0	½ 1 1 1 ½ 0 0 0 0 0
0 0 1 1 1 1 0 0 0 0	0 1 1 ½ 2 1 ½ ½ 0 0
1 1 ½ 1 ½ 1 ½ 1 0 0	0 1 2 2 2 1 0 0 0 0

It seems, therefore, that tentatively we may conclude that in a considerable proportion of cases of epidemic encephalitis, there is a negative colloidal gold chlorid curve, while in the remainder of cases in which a

10. Tilney, F., and Howe, H. L.: Epidemic Encephalitis, New York, 1920, p. 105.

11. Davis, T. K., and Kraus, W. M.: Am. J. M. Sc. **161**:109 (Jan.) 1921.

12. Nixon, C. E., and Sweetser, T. H.: Am. J. M. Sc. **161**:845 (June) 1921.

reduction occurs, the reaction is extremely variable sometimes presenting a tabetic, at others a paretic, meningitic, and at times a syphilitic curve. Judging by available information, therefore, only a small percentage of the curves of epidemic encephalitis fall entirely within the "poliomyelitic zone." Accordingly, it may be stated that while a mild syphilitic curve may indicate either one of the two diseases, a negative reaction, a paretic or meningitic curve, would be very strongly indicative of epidemic encephalitis, and as these latter are the usual reactions encountered, the test should be of distinct value in most questionable cases of differential diagnosis.

To realize the full value of this reaction in the diagnosis of poliomyelitis it must be taken into consideration with the history, physical findings and other laboratory data, in each case. It is a laboratory test and as such is subject to a personal equation of possible error, and it would

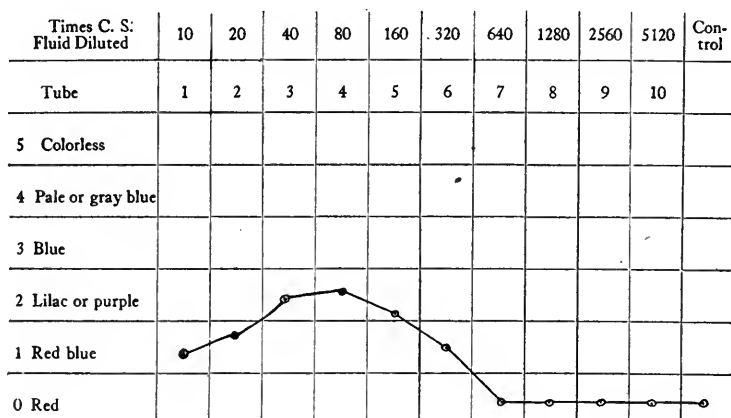


Fig. 5.—Average curve in fatal cases.

be poor policy to rely on it alone to the exclusion of all other information. We must recognize, however, that with a spinal fluid properly collected and preserved and with the test carefully performed by one familiar and experienced with the reaction, it is the most valuable laboratory means we possess at the present time, for the recognition of Heine-Medin's disease.

SUMMARY

The colloidal gold test was performed on seventy-four spinal fluids obtained from twenty-one cases of acute epidemic poliomyelitis. The fluids were examined at intervals varying from the fourth to the one hundred and twenty-third day of the disease. The predominant type of the malady was the myelitic with, however, a high proportion of

cases presenting symptoms of moderate or marked polyneuritis. The curves obtained have been classified according to the week of the disease in which the spinal fluids were taken. On this basis, an average curve has been constructed for each week from the first to the eighth (Figs. 1 to 4). Likewise, an average curve has been prepared from the reactions obtained in the fatal cases (Fig. 5). Finally, in Figure 6, we have placed all the curves obtained in the very acute stage of the disease, and have constructed by their limitations what might be called a poliomyelitic zone. For comparative study the curves of other well recognized meningeal conditions have been placed in the same figure.

CONCLUSIONS

We have drawn the following conclusions from a study of the colloidal gold reaction in this series of cases.

1. There was always a reaction with colloidal gold solution in the case of every poliomyelitic fluid examined during the acute stage of the malady. This reaction was constantly in the same zone (syphilitic zone).

2. The average curves for the first and second weeks of the disease were very similar, and consisted in a gradually rising curve presenting a graduated increase in reduction in ascending dilutions of the spinal fluid, starting in the reddish blue area in 1:10, extending into the lilac or purple in 1:40 to 1:80, and then descending somewhat more abruptly into the reddish blue again in 1:160 and reaching the non-reducing or red color in 1:640.

3. In the latter weeks of the disease the average curve gradually subsided, reaching normal in a minor proportion of the cases (three out of ten) by the eighth or ninth week, while in the remaining seven (70 per cent.) cases the curve remained still elevated at the ninth week. In two cases examined later than the eleventh week, one in the fourteenth and the other in the eighteenth, the curve was still elevated in both.

4. We have found a fairly typical poliomyelitis curve present in one chronic case as late as five years after the initial attack. This patient had a history of several relapses.

5. Of the three cases in our series, in which the curve reached normal before the end of the eighth week, this occurred on the twenty-eighth, fifty-third and fifty-fifth day, respectively. It is, therefore, exceptional for the reaction to become normal before the end of the fourth week of the disease.

6. When the curve has once reached normal, it has not been elevated again in the three cases in which this was determined.

7. Cases presenting a persistence of the very acute curve of the first few weeks up into the ninth week or beyond, commonly present at this time either considerable residual paralysis with slight, moderate or marked polyneuritis, or else slight paralysis with a polyneuritis, which still is or has been very marked. A definite persistence of the acute hydrocephalus commonly remains in these cases.

8. We are strongly inclined to believe that there is a relationship between the duration of the positive colloidal gold curve and the acute inflammatory stage of the malady, so that when the reduction of gold chlorid becomes normal, the acute period of the disease is over. If this is so, the reaction should be of value in determining when the rest of the acute period may be terminated, and the more energetic treatment by electricity and massage, etc., of the subacute stage begun.

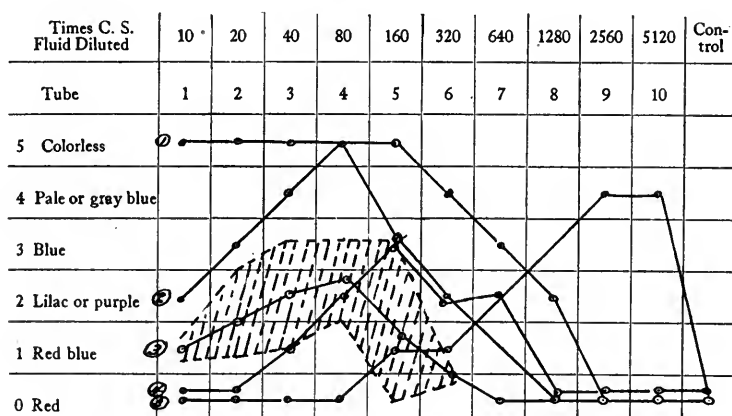


Fig. 6.—Comparative curve in (1) general paresis; (2) cerebrospinal syphilis; (3) Heine-Medin's disease; (4) tuberculous meningitis, and (5) epidemic cerebrospinal meningitis.

9. With the gradual subsidence of the colloidal gold curve there is usually a corresponding improvement in the patient's general condition, paralysis and meningeal symptoms. This relationship does not always hold true, and in patients who have had a marked polyneuritis, the curve may remain acutely elevated in the late weeks of the disease, despite the fact that the paralysis may have subsided entirely.

10. We found no close relationship, except in a general way, between the cytology and chemistry of the spinal fluid and the gold chlorid reaction. As the very acute symptoms subsided, the spinal fluid, in its chemical and cytologic contents, returned to normal. So, in most cases, does the gold chlorid curve return to normal, but more slowly, usually still remaining elevated at a period (eighth week) when

no other characteristic pathologic signs are to be found in the cerebrospinal fluid.

11. The average curve in the fatal cases, although showing a tendency to produce greater reduction, and to be prolonged slightly into the higher dilutions, did not differ sufficiently from that obtained in the nonfatal cases in the first few weeks, as to make the test of value in prognosis.

12. The gold chlorid curve began to fall in a few cases in the third and fourth week, and then was more elevated again in the ninth, tenth and eleventh weeks.

13. The reduction obtained in cerebrospinal syphilis will not usually be confused with that of poliomyelitis, except in a minor proportion of cases in which it runs rather low. In such instances the history and symptoms are so different as to cause no confusion in diagnosis, and the Wassermann test is available.

14. Typical curves of tuberculous meningitis should not be confused with those of poliomyelitis. Even the more unusual types of tuberculous meningitis curves rarely fall entirely within the poliomyelitis zone. If a curve is obtained from a clear fluid of a suspected poliomyelitis which is prolonged into the meningeal zone, a possible tuberculous meningitis should always be ruled out.

15. In the few instances in which poliomyelitis may be confused with epidemic encephalitis, the colloidal gold reaction may be of some use in differential diagnosis. The reaction in epidemic encephalitis is extremely variable, and a considerable proportion of cases present no reduction at all, while others yield a paretic, meningitic, tabetic or a very mild syphilitic curve. Often the latter two types (tabetic or luetic) fall entirely within the poliomyelitis zone. Hence we may say that in a given case, while such reactions may indicate either of the two diseases, any other type of reduction would point strongly to epidemic encephalitis. It would seem that the difference in reaction to gold chlorid is another point against the identity of the two infections.

16. Lange's reaction clearly differentiated in our series, the various forms of meningismus encountered from Heine-Medin's disease.

17. To realize the full value of this reaction, it must be taken into consideration with the history, physical findings and other laboratory data. We believe, however, that with a spinal fluid properly collected and preserved, and with the test correctly performed, it is the most valuable laboratory method we possess for the recognition of poliomyelitis, especially when the latter disease is sporadic or the type of case atypical.

The writers are indebted to Dr. W. W. Hala, Pathologist, Kings County Hospital, and Mr. F. J. Yonker, of the laboratory staff, for their generous cooperation in the laboratory portion of the work. Acknowledgment is made to Miss Meyers of laboratory staff and also Dr. S. Brody of the intern staff, Kingston Avenue Hospital, for assistance in the laboratory and clinical portion of the work.

THE CLINICAL VALUE OF INTRAPERITONEAL INJECTIONS OF SALT SOLUTION*

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PHILADELPHIA

Since the publication of the paper by Blackfan and Maxcy,¹ citing the advantages of the intraperitoneal route for the administration of saline solution to dehydrated infants, the method has been adopted widely and would appear to be one of the most valuable therapeutic procedures which has been proposed in recent years.

In 1914, Dandy and Rowntree injected solutions of phenolsulphone-phthalein into the peritoneal cavities of dogs and found that the dye appeared in the blood in from two to four minutes and in the urine in from four to six minutes while the quantitative output in the urine during the first hour amounted to from 40 to 60 per cent. of the amount of dye injected (0.6 mg.) This is fully as much of the dye on the average as is excreted after intramuscular injection and almost as much as though it had been injected intravenously. The result would suggest that absorption of isotonic solutions from the peritoneal cavity is so rapid as almost to equal the efficacy of intravenous injections.

In August, 1919, we began a study to make comparisons between various methods of administering water and to collect statistics on the intraperitoneal method. We first proved at necropsy that it was practically impossible to perforate the bowel by the sudden insertion of a needle through the abdominal wall, and that the peritoneal cavity of guinea-pigs could be injected repeatedly with isotonic salt solution, with or without dyes, without causing harm or discomfort.

In the comparison of different methods of introducing water, the five usual routes were used at first—by mouth, by bowel, intravenously, subcutaneously and by intraperitoneal injection. The first and last soon proved to be the only methods that permit of the safe and painless administration of water in sufficient amounts to be of real value, so that the others were practically discarded so far as the introduction of fluid per se was concerned.

The occurrence of vomiting and the disinclination of the child to drink are the chief practical objections to the oral method of administration. We found that the use of the nasal tube obviated the latter difficulty, and that water, introduced by this method, was retained quite often in spite of the fact that food would be vomited.

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* From the Medical Service of the Children's Hospital, Philadelphia.

1. Blackfan and Maxcy: *Am. J. Dis. Child.* **15:19** (Jan.) 1918.

A small, soft rubber catheter (No. 8 to 12 French scale) is lubricated with a stiff grease, such as petrolatum, several drops of liquid petrolatum are instilled into the nostril, and the catheter, with tube and funnel attached, is passed into the esophagus for a distance of from 20 to 25 cm. (from 8 to 10 inches) from the anterior nares. Next, the funnel is held under water. The absence of air bubbles insures that the catheter has not passed into the trachea. From 100 to 250 c.c. (from 3 to 8 ounces) of sterile water are then poured into the funnel. The whole procedure can be carried out so quickly that the water is in the stomach before the child has had much chance to resist. We feel that the introduction of the tube to a point well beyond the epiglottis, but not through the cardia, lessens the incidence of vomiting, and that the nasal route is less apt to induce gagging than is the passage of the tube by mouth. In 80 per cent. of the patients this use of the nasal tube did not excite vomiting at all—or at most, only occasionally. For example, one patient vomited only once during thirty-two treatments and another only twice in thirty-six treatments. Unless vomiting is induced, there is no shock and the discomfort is minimal. Free lubrication is essential when the tube is to be used often.

From 300 to 750 c.c. (from 10 to 24 ounces) of water in twenty-four hours can be administered without any interference with the taking of food, if a four-hour feeding interval is adopted and the water given from three to three and one half hours after a feeding. Many of our "tube" cases also received intraperitoneal injections of saline solution. By the early administration of water by nasal tube to patients with diarrhea it appeared that dehydration sometimes could be prevented.

Ohlmann's results² from the administration of water to thirty-four fasting infants and twenty children are of interest in this connection. Using from 200 to 400 c.c. water and collecting the urine at intervals thereafter, he found that infants less than 9 months old voided only from 69 to 92 per cent. of urine in proportion to the water ingested, whereas older children voided from 113 to 175 per cent. This would suggest that dehydration in infants can be influenced quite readily by water administered per oram but that diuresis would be proportionately less active.

INTRAPERITONEAL INJECTIONS

The description of the technic of this procedure need not be repeated. Marked abdominal distension appears to be the only contraindication. Efforts to relieve meteorism usually were sufficiently successful to enable us, in time, to inject any child who needed it.

2. Ohlmann: *Ztschr. f. Kinderh.* 26:291 (Oct. 8) 1920.

As a general rule, we were able to inject from 20 to 30 c.c. (from 5 to 8 fluid drams) for each 480 gm. (pound) of body weight, into infants under one year of age. At times much more than this proportion was injected, but 300 c.c. appears to be a maximum. The needle was withdrawn at once whenever disturbance of pulse or respiration occurred. Occasionally a temperature reaction was observed within three hours, which quickly subsided, except in the event that it merged into the pre-agonal rise seen in some of the desperately ill patients. It is impossible to believe that the injection itself caused these fatalities. Occasionally, there would be a leak of solution through the puncture wound after the needle had been withdrawn. This was usually checked by firm pressure for a few minutes or by a sterile gauze and collodion dressing. In one instance the leak continued for twelve hours, requiring frequent changes of a sterile dressing, but without any serious consequences. Apparently this was due to the use of too large a needle.

In a few cases glucose in 5 per cent. solution was injected in place of saline solution, but this was followed, at times, by such distress and peritoneal irritation, with rise of temperature, as to lead us to abandon its use.

The majority of the cases belonged to the group of gastro-intestinal disturbances with diarrhea. Fifty-seven patients had been acutely ill two weeks or less before admission to the hospital, and twenty-two had been ill more than two weeks. Most of these seventy-nine cases showed more or less intoxication. The mortality was 64.5 per cent. Twenty-six cases were diagnosed infantile atrophy but more or less diarrhea was present. The mortality among these was 61.6 per cent. Two premature infants and one with double otitis media and diarrhea died. Seven infants admitted for regulation of feeding on account of diarrhea and one with pyelitis recovered.

The 116 patients received 352 intraperitoneal injections of physiologic solution of sodium chlorid. The actual amount of fluid injected in the different weight groups shows a relatively larger amount for the youngest children. This can be seen by referring to Chart 1 in which it is shown that the infants weighing between 2 and 3 kilos (average, $2\frac{1}{2}$ kilos) received more than one half the amount given to those who weighed from 4 to 5 or even from 5 to 6 kilos. It is conceivable that we not only met but exceeded the fluid requirements of the small babies.

Comparison Between the Number of Injections and the Mortality.—Chart 2 shows, in general, a rise in the death rate as the number of injections given in each case increases—this, in spite of the fact that in the first two groups, members of which received only one or two injections, we included the desperately ill patients who succumbed within forty-eight hours after admission. It suggests either that water

alone cannot save the more chronic types or that the exhibition of water carries into the "chronic class" some patients who would have died earlier without it. A third explanation might be advanced that the intraperitoneal injections were harmful per se. This is negated by the experience in individual cases. For example:

H. L., aged 19 months, had been ill with ileocolitis ten days; weight, 9,772 gm. (21½ pounds).

From September 16 to October 19, he received eighteen intraperitoneal injections, during which time his weight fell to 7,366 gm. (16¼ pounds). In addition to the injections he received glucose, glucose and acacia and physiologic solution of sodium chlorid intravenously. On discharge in December he had almost regained his original weight. None of those who saw him doubted that he owed his recovery to the injections, since his diarrhea and vomiting were so severe as to prevent his retaining any nourishment or fluid for days at a time.

J. T., aged 4 months, had been ill since birth. She was a markedly dehydrated infant with acute diarrhea. Admission weight, 3,864 gm. (8½ pounds).

From November 22 until December 6 she received eight intraperitoneal injections, regaining her admission weight on the latter date.

TABLE 1.—COMPARISON OF MORTALITY WITH TOTAL GAIN, LOSS OR STATIONARY WEIGHT* DURING PERIOD OF INJECTIONS

	Number Patients	Recovered	Died	Mortality, per Cent.	Mortality, per Cent. Groups I and II Combined
Gain in weight.....	33	18	15	45	} 50
Stationary weight.....	11	4	7	63	
Lost weight.....	41	13	28	68.3	

* Weight taken 24 hours after last injection.

Comparison of the Weight with the Mortality.—Table 1 shows the weight taken twenty-four hours after the last injection, compared with the weight on admission, and the mortality. As most of the injections were given daily until the patient was out of danger or moribund, the gain in weight represents, in large part, the increment afforded by water per se as well as the ability of the patient to retain the fluid. The mortality of 50 per cent. in patients whose weight was stationary or had increased, and 68.3 per cent. in those who had lost weight corresponds quite closely to the results obtained in McLean and Lang's cases.³

Comparison Between the Number of Stools and the Mortality.—The serious results of the continuance of diarrhea scarcely need any emphasis but the graphic picture presented in Chart 3 gives a visualization which would seem to have some value in prognosis. When the stools continue to average six or more in twenty-four hours after the

3. McLean, S., and Lang, C. A.: Am. J. Dis. Child. 19:359 (May) 1920.

patient is admitted to the hospital and properly cared for, a very high percentage of fatalities may be expected.

DISCUSSION

The total mortality in the hospital among the 116 patients was 60.3 per cent. Every patient discharged as "recovered" left the hospital in good condition. Cases recorded on the history as "unimproved" were not included in this series.

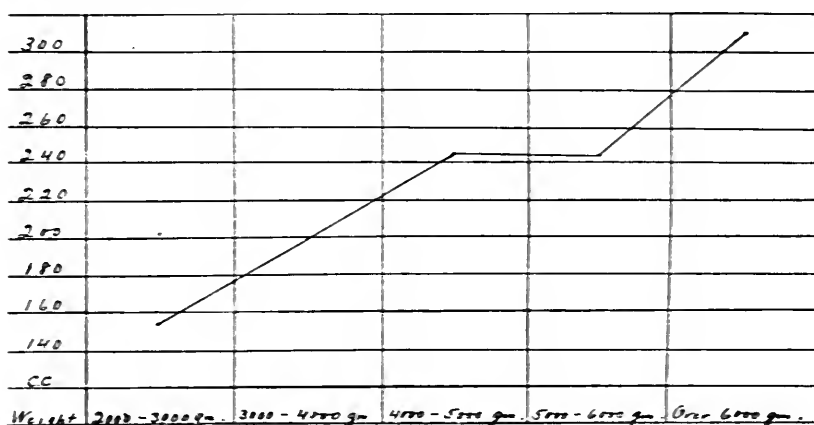


Chart 1.—Comparison of amount of saline injected with body weight.

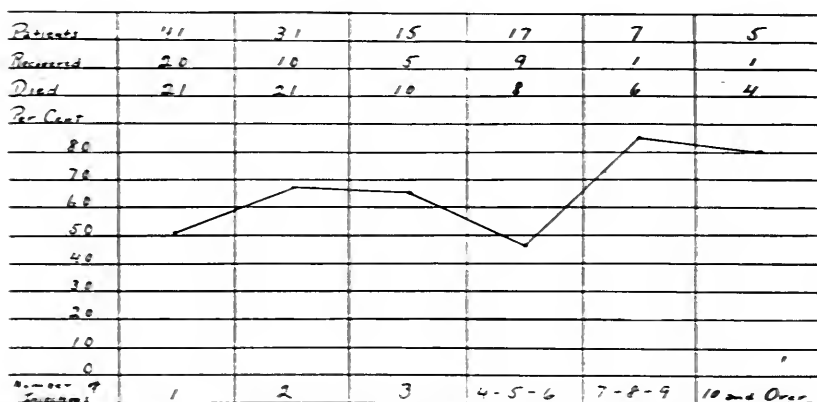


Chart 2.—Mortality compared with number of injections.

The method used for determining the degree of dehydration was purely clinical, based on the elasticity and resiliency of the normal skin and subcutaneous tissues. When these are pinched into a fold, they resume their previous shape and location as soon as they are released from the fingers. The delay in the time of this return which

is seen when the skin of dehydrated infants is pinched, we recorded as one, two or three plus dehydration, depending on the degree. Comparing the degrees of dehydration recorded at the beginning of treatment, with the mortality, we find that in cases showing 3 plus dehydration the mortality was 70 per cent.; in cases showing 2 plus dehydration, the mortality was 60 per cent., and in cases showing 1 plus dehydration, the mortality was 51 per cent. Among the forty-six patients who recovered, thirty-five showed complete return of normal resiliency of the skin, in six the end-result was not stated and in five the dehydration on discharge was recorded as 1 plus, having improved from 2 or

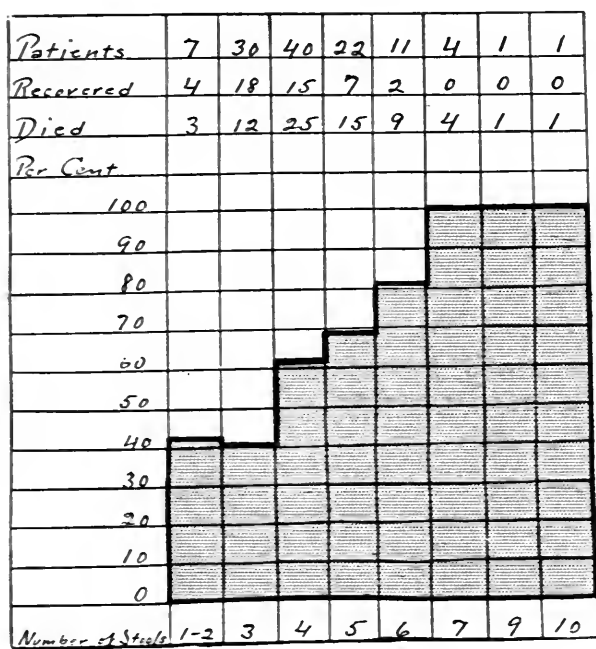


Chart 3.—Mortality compared with average number of stools during illness in the hospital.

3 plus. Among the seventy fatalities the notes on dehydration at the time of death showed: Dehydration same as on admission, 30 cases; dehydration more than on admission, 14 cases; dehydration less than on admission, 19 cases; dehydration entirely relieved, 5 cases; dehydration end-result not stated, 2 cases.

The factor of personal equation in such an empirical method of determining dehydration makes for considerable error but these results confirm the fact that can be demonstrated accurately by a study of blood volume, refractive index, etc., that relief of the anhydremia alone will not cure the worst types.

Necropsies.—In nine of the fatal cases the total of injections was twenty-eight (fourteen in one case), and the necropsy showed that no injury had been done to the peritoneum or to any of the abdominal organs or structures. In seven of the nine cases, in which death had occurred from twelve hours to seven days after the last injection, the peritoneal cavity contained no fluid. In one patient, who had died four hours after receiving 150 c.c. of fluid, the peritoneal cavity contained about 10 c.c. of clear straw colored fluid. In another patient, who died from twelve to twenty-four hours after receiving 500 c.c. of fluid, about 250 c.c. of fluid was found.

Comparison of Results in 1919 with Those in 1920.—The mortality was 81 per cent. in 1919 and 48.6 per cent. in 1920. The improvement may have been due, in part, to a difference in the type of cases, as only in the worst cases were intraperitoneal injections made at the beginning of our study. The atmospheric conditions and the methods of feeding were approximately the same in both years. It was believed that the more extensive use of glucose or of glucose with acacia by intravenous injection in 1920 also might have been a possible factor, but it was found that the mortality among twenty-one patients who received such injections was 71 per cent. as compared with the general

TABLE 2.—ANALYSIS OF CASES IN WHICH SALINE SOLUTION WAS INJECTED

	Year	Number Patients	Average Amount Injected, C.c.	Maximum	Minimum
Recovered.....	1919	8	260	450	150
	1920	31	169	315	75
Died.....	1919	34	293	650	100
	1920	34	187	325	100

mortality of 48.6 per cent. Judging from certain individual cases we are inclined to believe, however, that the amount of saline injected intraperitoneally in 1919 often was too large. Excluding nine cases in infants over 1 year of age who received the largest amounts of saline on account of their size, the findings were as shown in Table 2. Averages cannot be accepted as applying to individual cases but the indication is plain that the amounts of fluid injected in 1919 were considerably larger than in 1920. It is our practice at present not to give more than 150 c.c. for babies weighing less than 4 kilos, with 300 c.c. as a maximum.

SUMMARY

The forced ingestion of water by nasal tube deserves a more extensive trial in cases of diarrhea as a preventive, before anhydremia develops, and, in conjunction with intraperitoneal injections, as a curative measure. Other routes for the introduction of water rarely will be needed.

The optimum amount of fluid to be administered by mouth and especially the amount to be injected into the peritoneal cavity, should be determined more accurately. At present we feel that intraperitoneal injections should not exceed 300 c.c. and that 150 c.c. administered more frequently, if necessary, is a safer procedure for infants weighing less than 4,000 gm.

Puncturing the peritoneal cavity seems to be a safe procedure, provided the bladder is empty, distention is not extreme and a rigidly aseptic technic is employed.

There is need for a reliable clinical measure of the degree of dehydration. The lack of resiliency in the skin and subcutaneous tissues seems to give a reasonably accurate indication, but it should be controlled carefully by tests of the blood volume, blood flow and protein concentration.

Dehydration in itself must be an important factor in producing symptoms and in determining the outcome, but it cannot be held solely responsible for the deaths in many of the cases. The bad result of the continuance of diarrhea, however, is as sure now as it was before dehydration was adequately recognized.

HEMATOMAS IN THE HEART VALVES OF CALVES *

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The presence of hematomas in the heart valves of new-born calves is today a widely known fact. Nevertheless, a survey of veterinary literature reveals only brief references, and, since in these the microscopic structure and possible origin of the hematomas have not been discussed, a study of these two points was undertaken. The literature describing hematomas in the heart valves of children was not consulted until the conclusion of the work on calves.

Kitt¹ describes the hematomas as being bladders of blood or serous fluid, varying in size from a lentil to a pea, situated between the flat endocardial folds of the artioventricular valves, and raised somewhat above the surface of the valve. He gives no references but cites Glage and Kläger, whose observations agree with his own on slaughtered swine and young calves, and Gibson who had seen similar small cysts in lambs. Ostertag² refers to the hematomas as true hemorrhages, which he considers normal and not infrequent in young calves. He also cites Kläger. In 1914 Egge³ published a short paper and in the same year another reference appeared in the textbook of Jost and Koch.⁴ The latter add nothing to the description of Kitt. From 1905 to the time of publication, Egge examined the hearts of young calves slaughtered in the abattoirs under his care, and in the heart valves of almost all the animals he found extravasations consisting, in part, of sharply defined swollen blood tumors varying in size from a pinpoint to a pea, and in part of more or less large level areas of blood in the tissue of the valve. These were situated in the region of attachment of the chordae tendinae. He also examined the hearts of fetuses and prematurely born calves with positive results. He did not find hemorrhages in calves that had lived four or five weeks, and concluded that the blood must be absorbed during the first weeks of extra-uterine life. He offers no explanation of the presence of these hemorrhages and refers only to the work of Ostertag. He also examined the hearts of foals, young swine, and lambs, but never found any extravasations.

* Received for publication, Oct. 17, 1921.

* From the Department of Animal Pathology of The Rockefeller Institute for Medical Research.

1. Kitt, T.: *Pathologische Anatomie der Haustiere* 2:310, 1906; *Ibid.* 2:337, 1911.

2. Ostertag, R. von: *Handb. d. Fleischbeschau*, Stuttgart 1:263, 1910.

3. Egge, G.: *Berl. Tierärztl. Wchnschr.* 4:63, 1914.

4. Jost, J., and Koch, M.: *Krankheiten junger Tiere im Vergleich mit Kinderkrankheiten*, 1914, p. 631.

We have been unable to find the original references of Glage, Kläger and Gibson.

Similar hematomas are of frequent occurrence in the heart valves of new-born and young children, and they have been seen in the human fetus and in still-born children. The literature has been carefully reviewed by Wegelin,⁵ consequently only a brief summary is given here. Luschka,⁶ who cited Elsässer⁷ as the first to mention hematomas in the heart valves, accurately described their macroscopic appearance and attributed their origin to hemorrhage, due to ruptured vessels, into the soft tissue of the noduli albini. Parrot⁸ also thought that they were formed through the rupture of intravalvular blood vessels after birth but regarded the noduli albini as resulting from the organization of this hemorrhage. In 1898 Berti⁹ published an entirely new view. He discovered the endothelium lining the blood cavities and concluded that they were not hematomas but varicose vessels or blood cysts due to changes in the pre-existing blood vessels. He also examined a number of animal hearts and pictured a cyst in the atrioventricular valve of a four-weeks-old lamb. The same year Haushalter and Thiry¹⁰ described a connective tissue layer and not endothelium surrounding the blood cavities and again named them hematomas. They saw no vessels in the valves in the neighborhood of the hematomas, but in serial sections traced a connection between them and the cavity of the ventricle. They thought the blood was forced into the bays on the under surface of the valve at birth and in earliest infancy, and that the soft tissue gave way before the pressure allowing the blood to penetrate the valve. This blood was then dammed back in the tissue during the ventricular systole through the stretching of the valve and the pull of the chordae tendinae. This view was severely criticized by Berti.¹¹ Fahr¹² examined the hearts of children during the first months of life and in almost every case found hematomas in the valves. He also found them in most of the fetuses he examined from the sixth month of development. Like Berti⁹ he saw the endothelium lining the blood cavities and thought them vessel ectases. Wegelin⁵ described the histologic structure in great detail and figured serial sections to demonstrate his theory of the formation of the hematomas. He agreed with Haushalter and Thiry that they were formed by the

5. Wegelin, C.: *Frankfurter Ztschr. f. Path.* **2**:411, 1909.

6. Luschka, H.: *Virchows Arch. f. path. Anat.* **11**:144, 1857.

7. Elsässer: *Bericht über die Ereignisse in der Gebäranstalt des Catharinen-hospitals*, Stuttgart, 1844.

8. Parrot, J.: *Arch. de physiol. norm. et path.* **1**:538, 1874.

9. Berti, G.: *Boll. delle sc. med. di Bologna*, 1898, pp. 343, 479, 581; *Referat, München. med. Wchnschr.*, 1898.

10. Haushalter, P., et Thiry, Ch.: *Arch. de méd. expér.* **10**:558, 1898.

11. Berti, G.: *Arch. f. Kinderh.* **31**:371, 1901.

12. Fahr: *Virchows Arch. f. path. Anat.* **184**:274, 1906.

forcing of the blood against the valves, but he also recognized the endothelial lining of the cavities and said they arose through the widening and secondary cutting off of some of the bays which lie normally on the ventricular side of the valve where the chordae tendinae are attached. Just after Wegelin had finished his investigation, but before the publication of his results, two further papers appeared. Meinhardt¹³ had arrived independently at practically the same conclusions as Wegelin. Hammes¹⁴ also saw the narrow canals connecting the blood cavities with the ventricle, but agreed with Berti in considering the hematomas ectases of true vessels. Also he thought they had no connection with the coronary system but constituted a second type of valve vessel serving to nourish the valves during the last third of fetal life and the first year of extra-uterine life.

During the past five years accumulations of blood have been seen very frequently in the tissues of the atrioventricular valves in the fetuses and young calves examined in this institute. These have not been found in the semilunar valves of calves by us or by Egge, but they have been recorded by a number of pathologists as occurring in these valves in children. As stated by Egge, these accumulations of blood are of two distinct types. There are clearly defined hematomas varying in size from a pinpoint to a large pea; the largest one sectioned had a diameter of 6 mm. They are usually subcircular, but frequently a few very small hematomas are scattered close around the border of the larger ones giving a false appearance of an irregular edge. There may be one or several in a valve, and occasionally we have seen a number of small ones clustered together, resembling somewhat the surface of a blackberry and extending over the greater part of the valve. They are slightly raised above the atrial surface but not so much so as those in children as described by Berti and Wegelin, and are visible from both surfaces of the valve. They are usually blackish-red in color, but sometimes they are bright red. Most are firm to the touch and evidently quite filled with blood, but occasionally some are not fully distended and are soft to the touch, so that their form changes somewhat under pressure. The second type is hemorrhage over a level area of irregular outline and not at all elevated above the surrounding surface; some of these have been found bright red and others blackish-red in the fresh state. In one case of a calf, which died when two days old, hemorrhage extended around the entire set of valves of the right side of the heart, while numerous hematomas were present in the valves of the left side. Both types are situated among the attachments of the chordae tendinae.

13. Meinhardt, H.: *Virchows Arch. f. path. Anat.* **192**:521, 1908.

14. Hammes, F.: *Virchows Arch. f. path. Anat.* **193**:238, 1908.

Valves from the hearts of eight calves, varying in age from one day to three months, have been studied microscopically by means of serial sections stained with eosin and methylene blue, hematoxylin and eosin, and by the Gram-Weigert method. The two types of hemorrhage present very distinct pictures. In the case of the hematomas our findings are similar to those of Wegelin, although our interpretation of them is somewhat different. In every case there was a clearly defined cavity lined with a single layer of endothelium and well filled with blood cells among which the mononuclear and polynuclear elements were present in normal numbers. In a few cases in which the cavity was much distended there was crowding of the surrounding tissue which gave a false appearance of a connective tissue capsule. The largest hematomas extended into the region of the muscle at the attached border of the valve. In no case were true blood vessels found communicating with the hematomas, but their connection with surrounding slender endothelial-lined channels and clefts could frequently be traced through successive sections, while at other times chains of endothelial cells with large dark-staining nuclei and a narrow border of cytoplasm were the only trace of original channels. Neighboring hematomas were often seen to become confluent with one another and form large blood-filled cavities which in later sections again divided into small cavities. In children Haushalter and Thiry described the disappearance of the hematomas through destruction of the red cells, accumulations of fibrin, invasion of the blood by round cells, and by budding. Wegelin also saw the hematomas obliterated through the changing of the red cells into a hyalin mass and its subsequent organization by the outgrowth of endothelial and connective tissue cells. In the oldest calves studied, traces of budding of endothelial and connective tissue cells were seen in the hematomas, but never such accumulations of fibrin as Haushalter and Thiry described or the collections of pigment mentioned by them and by Wegelin. These accumulations of blood are either organized or absorbed, since they are not found in older animals.

A study of serial sections of the level areas of blood showed that they were due to an extravasation of blood into the tissue of the valve. Where much blood had escaped the structure of the valve was entirely concealed but in other cases numerous capillaries and clefts were seen. In none of the sections was there any evidence of rupture and the blood had apparently escaped from the vessels by diapedesis. Such a condition, while tolerably frequent in calves, is evidently unusual in children, since Wegelin alone mentioned small hemorrhages under the endothelium and in the tissue surrounding small hematomas. In none of the cases studied have any other pathologic conditions been found in the valves.

In the majority of the calves having blood accumulations in the heart valves punctiform hemorrhages are frequently seen in the alimentary tract, particularly in the fourth stomach and in the pyloric and ileocecal valves and rectum. Their importance, owing to their opening a way of infection, and their possible connection with the hematomas and hemorrhages of the heart valves will be discussed in a later paper.

DISCUSSION

Three different views have been stated concerning the source of the hematomas found in the heart valves of children: first, that they were the result of hemorrhage; second, that they were ectases of true blood vessels; and third, that they were the result of the forcing of blood into the soft tissues of the valve during the ventricular systole. Each view has with various modifications been supported by a number of investigators and both Berti and Wegelin have discussed the question at considerable length. The present study has suggested another origin.

Since hematomas are found only in the valves of fetuses and very young animals their origin must be looked for in the course of the development of the heart. Minot¹⁵ first pointed out that in all vertebrates there occur two types of blood vessels with endothelial walls only, namely, capillaries and a second form which he named sinusoids. The facts of the development of the cardiac trabeculae were already well known, but Minot first interpreted the condition as a sinusoidal circulation and as showing the primitive circulation of the heart itself. Only later when the coronary arteries develop is a true capillary circulation formed. His study of embryos led him to conclude that for a time the nourishment of the heart is direct, from its own contained blood. Lewis¹⁶ confirmed Minot's work and showed both in fish and rabbits that the heart has a superficial capillary and a deep sinusoidal circulation wholly different in their development. In adult fishes and amphibians the sinusoids remain highly developed while in mammals they undergo a regression. According to Lewis many sinusoids are "reduced to strands of endothelium without lumen. Others are retained as slender vessels opening into the ventricle at both ends. These are probably the source of those vessels of Thebesius described by Langer¹⁷ in adult human hearts, as associated with the papillary muscles and communicating at both ends with the ventricle. Other sinusoids remain large, and seem to anastomose with the coronary vessels suggesting the free communication between the ventricles and coronary veins found by Pratt¹⁸ in the heart of calves."

15. Minot, C. S.: *Proc. Boston Soc. Nat. Hist.* **29**:185, 1900.

16. Lewis, F. I.: *Anat. Anz.* **25**:261, 1904.

17. Langer, L.: *Sitz.-Ber. d. Akad. d. Wiss. Wien.* **82**:25, 1881. Quoted by Lewis.¹⁶

18. Pratt, F. H.: *Am. J. Physiol.* **1**:86, 1898. Quoted by Lewis.¹⁶

In the course of their development the anlagen of the valves are connected with the trabeculae of the ventricles. The muscle bundles on the atrial surface of the valve anlagen pass toward the ventricles and are apparently continuous with the ventricular bundles so that for a time the valve cusps consist partly of endocardial growths and partly of musculature. At first the endocardial growths greatly surpass the muscular and later the trabeculae which pass from the spongy substance of the ventricles to the valves increase greatly and the central portions of the valves come to project further into the lumen. The trabeculae separate from the corticalis and pass more toward the center and at the same time the musculature of the valves undergoes considerable development. Later this musculature of the valve is replaced by connective tissue and elastic threads and the trabeculae become transformed into chordae.

During the period of intimate connection between the trabeculae and developing valves the sinusoidal circulation doubtless penetrates and nourishes the latter. It seems reasonable then to infer that the hematomas are vestiges of the primary sinusoidal circulation of the heart, and that the strings of cells, slender vessels, and smaller clefts seen in all sections of valves are also vestiges of sinusoids and, as Lewis suggests, may be the vessels of Thebesius. Among previous workers only Hammes suggested that the hematomas and small vessels might be a distinct circulation apart from the coronary circulation.

In studying serial sections of the true hemorrhages, capillaries and small clefts congested with blood were seen wherever the hemorrhage was not so abundant as to conceal all the structure of the tissue. In successive sections these vessels could not be traced to any connection with larger vessels toward the base of the valve, so it must be inferred that they are some of the vessels of Thebesius and that the hemorrhage has taken place by diapedesis through their walls.

The existence of such an independent inner circulation in the heart may also account for the great variety of opinion as to whether the atrioventricular valves are vascular or not. The most recent work we have seen is that of Argaud.¹⁹ He concluded that in oxen, as in man, blood vessels are sometimes present in the valves, and that in horses they are always present.

Hematomas have not been recorded as occurring in the semilunar valves in animals, and in children much less frequently in these than in the atrioventricular valves. Wegelin considered this to be the result of the small number of invaginations on the surface of the valve and the small quantity of elastic threads in the tissue, while in accordance with our hypothesis it would be due to the great restriction of trabeculae in the atria. In spite of the fact that the small quantities of blood

19. Argaud, R.: *Compt rend. Soc. biol.* **62**:812, 1912.

invariably present in the bays between the chordae tendinae and communicating with the cavity of the ventricle suggest the formation of the hematomata by the forcing of the blood into deeper bays as Wegelin and Meinhardt have concluded, their interpretation as remains of the primary sinusoidal circulation seems a more natural process.

These cavities filled with blood are not true hematomas, and some writers have suggested that they be called blood cysts. Only a microscopic study of the valves of fetuses at different stages of development will actually prove our hypothesis of their origin as sinusoids and till then we propose to retain the name hematoma.

CONCLUSIONS

Hematomas and hemorrhages are of frequent occurrence in the atrioventricular valves of fetuses and young calves. Both are situated in the region of attachment of the chordae tendinae and may occur in the same valve.

The hematomas are subcircular cavities lined with a single layer of endothelial cells and may be sinusoids which persist from the primary sinusoidal circulation of the heart.

The hemorrhages apparently occur by diapedesis from the vessels of Thebesius.

No other pathologic conditions have been found in the affected valves.

EFFECT OF TONSILLECTOMY ON NUTRITION IN TWELVE HUNDRED CHILDREN *

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Tonsillectomy has become a common operation. The indications for this procedure differ. Until recently tonsils were removed only if they were obstructive or presented definite evidence of infection. Marked improvement followed the removal of such tonsils in most instances. In recent years the operation has been recommended as a prophylactic procedure, and so-called potentially diseased tonsils are removed. Much is expected from a tonsillectomy and I believe rightly so if the tonsils are at fault. One is so often impressed with the marked improvement in nutrition after such an operation that the influence of the operation on nutrition cannot be overlooked.

In a clinic in which ten thousand children were subjected to the operation, a study was made of twelve hundred to determine the effect of the operation on nutrition. These children received more or less uniform care having all been operated on in one clinic by the same surgeons and selected for operation by two physicians who followed a uniform standard for the designation of cases for operation. A careful history was taken of each child, and the definite complaints of the child were charted. All the cases were so-called extreme cases with obviously diseased tonsils and adenoids, or presenting complaints definitely referable to a possible focus in the tonsils. Practically all these children were operated on in the summer of 1920 and reexamined from nine to twelve months later. The estimation of the child's nutrition is based on the height—weight relationship. When the children appeared for operation they were measured in stocking feet and weighed without outside clothing. The same children were similarly measured and weighed at this subsequent examination. Weights and measurements were compared with the table of average weight and height measurements published by Dr. Emerson for the Nutrition Clinics for delicate children.

The children operated on represented the so-called urgent cases. The reasons for operation varied. Many children had large obstructive tonsils and adenoids, others obviously infected tonsils while a few showed no evidence of diseased tonsils but had recurrent infections in the head which could be attributed to the tonsils. There seemed to be a definite indication for operation in each case.

* Received for publication, Nov. 11, 1921.

* From the Nose and Throat Department of the Rochester Dental Dispensary.

The 1,200 children studied ranged in age from 3 to 15 years. These children presented themselves for operation because of throat symptoms and not because of malnutrition and thus do not represent necessarily a group of malnourished children. No effort was made to place these children in a nutrition class though the school nurse or social service worker had instructed them in habits of life which might have some bearing on their nutritional improvement.

The children were grouped into three classes: (1) Those who were 10 per cent. or more overweight; (2) those who had normal weight or were less than 7 per cent. underweight (so-called borderline cases); (3) those who were 7 per cent. or more underweight. At the time of reexamination the same children were reclassified to determine their nutritional status after the operation.

TABLE 1.—NUTRITIONAL STATUS OF CHILDREN AT TIME OF OPERATION

	10 Per Cent. or More Overweight		Normal Weight or Borderline Cases		7 Per Cent. or More Underweight	
	Number	Per Cent.	Number	Per Cent.	Number	Per Cent.
Boys.....	37	3.1	323	28	185	15
Girls.....	40	3.9	381	31	224	19
Total.....	87	7	704	59	409	34

In this group of 1,200 children the percentage of malnutrition (34) was about the same as is being found in the schools throughout the city. Though an equal number of girls and boys were examined, it was noted that malnutrition existed in 4 per cent more girls than boys. The age distribution is not significant. More children were underweight between the ages of 5 and 9 than in later childhood.

TABLE 2.—NUTRITION STATUS OF CHILDREN NINE MONTHS AFTER OPERATION

	10 Per Cent. or More Overweight		Normal Weight or Borderline Cases		7 Per Cent. or More Underweight	
	Number	Per Cent.	Number	Per Cent.	Number	Per Cent.
Boys.....	57	4.7	425	35.5	70	5.9
Girls.....	67	5.5	461	38.4	120	10
Total.....	124	10.2	886	73.9	190	15.9

A reexamination of these children from nine to twelve months after the operation showed a marked improvement in the nutrition. Generally, it can be stated that when the nutrition improved, the symptoms for which the child was operated on were relieved. In order to determine the net gain in weight, the growth of the child had to be taken into consideration. The weight was computed for the child's height, measured as at the original examination, and the entire group reclassified. It was found that in the group of 1,200 children the per-

centage of malnutrition, or those who were 7 per cent. or more underweight, was 15.9. In the normal classification were 73.9 per cent. of the group, while 10.2 per cent. were 10 per cent. overweight.

An analysis of the 15.9 per cent. representing 190 children who failed to attain their normal weight shows that other factors besides diseased tonsils are at fault. Enlarged cervical glands following tonsillectomy were found in fifteen cases. Pertussis, bronchitis or some other infection, followed the operation in others. Poor home control and improper diet could be traced to others. More careful examinations of this group will need to be made to determine their failure to gain properly.

It is significant, however, that about 50 per cent. of the 409 underweight children should have attained their normal weight for their height in a period of nine months. Without any other efforts to improve their nutrition it seems fair to assume that diseased tonsils and adenoids were at least partly responsible for this condition. It must be stated that not all children improved their status or even held their own, for 7 per cent. of the total number were relatively in poorer nutrition at the time of reexamination than at the time of operation. But of the entire group 219 children showed a very marked nutritional improvement.

TABLE 3.—NUTRITIONAL IMPROVEMENT MADE AFTER OPERATION

	Number Examined	Number Overweight	Number Nor- mal Weight	Number Underweight
At time of operation.....	1,200	87	704	409
Nine months after operation.....	1,200	124	886	190

CONCLUSIONS

1. Among 1,200 children operated on for diseased tonsils and adenoids there was 34 per cent. malnutrition (7 per cent. or more underweight).

2. Reexamination from nine to twelve months later showed a reduction of malnutrition to 15.9 per cent.

3. Diseased tonsils and adenoids do not necessarily impair nutrition, as evidenced by 66 per cent. of children showing normal weight according to height.

4. Diseased tonsils and adenoids are undoubtedly a factor in malnutrition, as evidenced by the marked improvement in 219 children of the group.

CLINICAL DEPARTMENT

REPORT OF A CASE OF GANGRENE OF THE FEET FOLLOWING DIPHTHERIA *

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BROOKLYN

Peripheral gangrene following diphtheria is of very rare occurrence. Ker¹ mentions the condition but states that he never saw a case. He refers to Rolleston,² who saw a case in 1910 and who was able to collect ten others from the literature at that time. Robbins³ published a review of twenty-five cases of peripheral gangrene following diphtheria. The next important contribution to the subject was a critical and exhaustive résumé of the literature by Bailey.⁴ No new case has been reported since. Our case is the fourth to be observed and reported in America, the previous ones having been published by Vedder (1879), Ward (1894) and Munn (1894).

REPORT OF CASE

History.—Abraham A., 6 years old, gave a history of having had a sore throat for four days without having received any medical attention. On the fourth day, a physician was called. He made a diagnosis of diphtheria and administered 15,000 units of antitoxin and advised removal to a hospital.

Examination.—The boy was admitted to the Kingston Avenue Hospital, April 26, 1920. He was poorly nourished and pale. Eyes and ears were negative. His throat showed an involvement of the fauces and pharynx, the membrane extending over both tonsils, uvula, posterior nares, nasopharynx and the pillars of the soft palate on the left side. Glandular involvement was moderate. The lungs were negative. The heart sounds were of good quality, rapid but no murmurs. The spleen was negative. The liver extended over to the left and could be felt about 2 inches below the free border of the ribs. He was given an additional 25,000 units of antitoxin intramuscularly.

Course.—Seven days after admission, the heart sounds became weaker in muscular tone and irregular. On the next day, he complained of severe pains in the left foot. There was a difference in the temperature between the two lower extremities, the left feeling colder to the touch. Purplish colored ecchy-

* Received for publication, Oct. 28, 1921.

* From the Kingston Avenue Hospital for Contagious Diseases, Department of Health.

1. Ker, C. B.: Infectious Diseases, Oxford University Press, London, Ed. 2, 1920.

2. Rolleston, J. O.: Brit. J. Child. Dis. 7:529, 1910.

3. Robbins, F.: Juvenile Peripheral Gangrene in Infectious Diseases; Diphtheria, Med. Rec. 94:620, 1918.

4. Bailey, L.: Occlusion of the Arteries of the Limbs in Diphtheria, Internat. Clin. 2:157, 1920.

motric areas were irregularly distributed over the skin of the left thigh and leg. These disappeared by the following day but the toes of the left foot seemed to be of a blue color as compared with the pink color of the right foot. The thigh and leg had become somewhat warmer to the touch. Sensation was lost in the lower half of the left leg and foot, and there also was an apparent weakness of the same limb which caused it to hang flaccid. The reflexes were altered, in that the knee jerks were absent on both sides, the plantar reflex was absent on the left but present on the right; ankle clonus was negative on both sides, Oppenheim sign was normal on the right side but no response was elicited on the left; no Babinski or Kernig on either side. The pain in the left leg and foot was severe enough to necessitate the administration of morphin.

Coincidentally with these local changes, the heart condition had become progressively worse so that on the twelfth day in the hospital there was a pronounced myocarditis with a gallop rhythm, reduplicated second sound and a tumultuous heart action. There were no murmurs. The throat was clear of any exudate but still gave a positive diphtheria culture. A posterior palatine paralysis with nasal regurgitation of fluids had developed. The child, however, was in an apparently comfortable condition.

Examination of the pulsation in Scarpa's triangle showed that it was present on both sides but not as pronounced on the left side as on the right. The popliteal pulsation was also not as definite on the left side as on the right.

The bluish discoloration of the left foot persisted, this being present on the dorsum and to a lesser extent on the plantar surface, being accompanied by a dilatation of the veins. The foot was swollen and waxy in appearance. The condition ameliorated with the establishment of a collateral circulation so that the foot became warmer to the touch and the color picture changed so that a few days later the dorsum presented two zones. From the ankle to the toes, the color was a deep cyanotic purple of uniform intensity, while just above and around this area was a zone of purplish red hyperemia. The deep purplish hue extended to the plantar surface. The cyanotic zones on both surfaces were swollen, edematous and hard to the touch.

Eight days subsequent to the involvement of the left foot, the boy experienced a sharp pain in the right foot. Within a day or two this was followed by a sensation of cold in the right foot and the appearance of irregularly distributed purplish areas on the dorsum. The foot became swollen. The toes became involved and then the heel. Within a few days, however, the cyanosis of the toes and dorsum of the foot gradually disappeared, but the discoloration on the heel remained, attaining the size of a silver trade dollar. The temperature on the right side gradually became lower than that on the left, especially from the knee down, the foot itself being almost ice cold. The cyanosis was not as pronounced as in the left foot, nor were the two color zones as definite. Within a week after the onset of the process in the right foot, the condition had improved to such an extent that the gangrene was limited to a small portion of the heel.

The process in the left foot became confined to the toes, a small portion of the plantar surface and 2 inches above the metatarsal phalangeal junction on the dorsum, the affected area being of a blackish purple color, hard in consistency and not painful. A sharp line of demarcation formed between this area and a surrounding one of a reddish pink. Within a month subsequent to the onset, the toes of the left foot showed a beginning desiccation, the dry gangrene also including a small portion of the plantar surface and some distance above the toes on the dorsal surface. The gangrene on the right heel was later confined to the skin and a slight area of superficial tissue.

Sloughing of the tissue ensued at the line of demarcation in both feet, resulting in a natural amputation of the gangrenous area in the right heel and a separation of the tissues down to the bone at the metatarsal phalangeal junction in the left foot. This process was permitted to continue for two months until the condition of the child had improved.

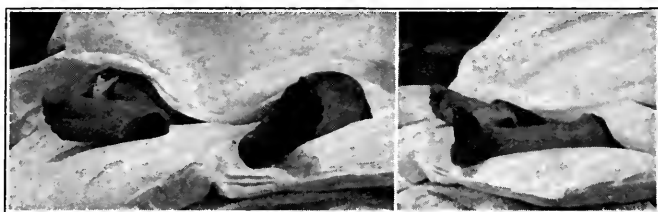
Operation.—August 30, about four months after the onset of the diphtheria, an operation was performed by Dr. Dangler, consisting of amputation through the metatarsal phalangeal joint of the left foot. By this time, the general condition and the cardiac lesion had both improved to such an extent that the gallop rhythm had disappeared and the myocardium assumed a stronger muscular quality.

The boy was discharged from the hospital within two weeks after the operation. At the present time, he is able to walk without any noticeable deformity.

Laboratory Findings.—Cultures: During his stay in the hospital throat cultures were positive for *B. diphtheriae* at the onset, while the nose cultures were always negative. At no time was any growth of diphtheria bacilli found in the blood. Three blood cultures were sterile. The Wassermann reaction was negative.

Blood: Red blood cells, 5,000,000; white blood cells, 16,600. Polymorphonuclears, 60 per cent.; lymphocytes, 39 per cent.; eosinophils, 1 per cent. Hemoglobin, 80 per cent. The coagulation time was four minutes.

The chemistry of the blood was studied by Dr. C. M. Anderson of the Long Island College Hospital: Urea nitrogen, 12 mg. per hundred c.c.; sugar, 76 mg. per hundred c.c.; urea, 25.68 mg. per hundred c.c.; uric acid, 3.1 mg. per hundred c.c.; creatinin, 1.6 mg. per hundred c.c.



Gangrene of heel of right foot and toes of left foot.

Urine: Urinalysis at the onset showed a trace of albumin with a specific gravity ranging from 1.010 to 1.030, always acid, sugar always absent, and occasionally pus cells, hyaline and granular casts. This all cleared up later.

Treatment.—This consisted of stimulation by means of whisky, camphor and epinephrin chlorid. Morphin was at times needed to control the pain. The lower extremities were encased in a hot air chamber which was arranged by fitting up a wire tent over which was placed the bed sheeting and a blanket to prevent the escape of the heat which was furnished by an electric bulb within the chamber.

DISCUSSION

The delay in obtaining medical aid permitted the local spreading of the diphtheritic membrane and the accumulation of the diphtheria toxin in the system. While it is not known if the gangrene in these cases is the result of a massive diphtheritic intoxication or a superadded infection by some other organism, it seems plausible to feel that in this case the late administration of antitoxin permitted an intense diphtheritic toxicity. In spite of the severity of the disease, diphtheria bacilli were never found in the blood in the three examinations made. That the diphtheria bacillus is not very often found in the blood in

diphtheria was shown by Rodelius, who found this organism in only three cases out of 187 (196 withdrawals and tests).

Our case, like others in the literature, occurred in the hypertoxic type of diphtheria in which symptoms of cardiac insufficiency had already developed and after the local throat symptoms had disappeared. The course was the typical one of myocarditis—sluggish circulation, low blood pressure and insufficient collateral circulation. It is very difficult to state positively whether the condition was due to a local thrombus as the result of a local acute arteritis or to a migrating clot originating in the heart. Bailly and Robbins think that the condition is due to a migrating clot following the myocarditis. Those who are interested in the controversy as to whether peripheral gangrene following diphtheria is due to a thrombosis or an embolus are referred to Bailly's recent paper on the subject.⁴

Surgical intervention was postponed in our case because we felt that the child's general condition at the onset was too critical to subject him to any operative procedure. Later, when his condition had improved and the line of demarcation had made its appearance, it was thought best to permit a natural amputation in the hopes of saving a larger portion of his foot. The results amply justified our waiting.

PROGRESS IN PEDIATRICS

RÉSUMÉ OF LITERATURE (1920) ON TUBERCULOSIS IN CHILDREN *

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CHICAGO

MODE OF INFECTION

J. W. ALLAN ¹ is of the opinion that antenatal tuberculosis is more common than is generally believed and that many children are born with "seeds" of the disease lying latent which at a later period of life give rise to manifest tuberculosis. He thinks the placenta offers the most likely portal of entry for the tubercle bacillus, and quotes Bonny, who says that, despite the normal appearance of the fetal organ and of the placenta, tuberculosis has resulted from inoculation of animals with portions of these tissues and with blood from the placental circulation. Allan thinks that to account for the subsequent development of tuberculosis in the animals inoculated these apparently healthy tissues must have contained some "seed" or inverted form of the tubercle bacillus.

M. DUBOIS ² adds the report of a case of intrauterine tuberculous infection to those already found in the literature. A woman suffering from miliary tuberculosis gave birth, prematurely, to a child. Forty-two days later she died and necropsy showed, besides the miliary tuberculosis, an old caseous tuberculosis of the left tube, of the endometrium, and a diffuse tuberculous peritonitis. The miliary tuberculosis originated either from a large tubercle in the right renal vein or from caseated tubercles found in the wall of the small uterine vessels.

The child, removed at once from the mother, developed poorly and died on the fifty-fourth day. The necropsy showed an old softened lesion in the right upper lobe with caseation of the right bronchial lymph glands, as well as a generalized miliary tuberculosis. The finding in the mother of a tuberculosis of the endometrium, which involved the site of the placenta and the age of the pulmonary and bronchial gland tubercles speak for an intrauterine infection either of haematogenous origin or due to aspiration of the amniotic fluid. The author

* Received for publication Dec. 10, 1921.

1. Allan, J. W.: Prenatal Tuberculosis, *Glasgow M. J.* **93**:1 (Jan.) 1920.

2. Dubois, M.: Intrauterine Tuberculous Infection, *Schweiz. med. Wchnschr.* **50**:772 (Aug. 26) 1920.

thinks the latter more probable because of the presence of the oldest lesions in the lung of the child and the findings in the uterus of the mother.

BACTERIOLOGY

A. STANLEY GRIFFITH³ has tried to ascertain the relative proportion of the human and the bovine types of tubercle bacilli in different kinds of human tuberculosis. Of twelve cases of tuberculous meningitis, ten were caused by the tubercle bacillus of the human type and two by that of the bovine type. In one instance the cow's milk supplied to the patient was found to contain virulent tubercle bacilli, indetical in cultural characteristics with the strain from the meninges of the child.

Of seventeen cases of phthisis, sixteen were caused by the human bacillus and one by the form of bacillus recently found in various kinds of human tuberculosis and in one case of simian tuberculosis. Of twelve miscellaneous cases (three of bone and joint tuberculosis, eight of glandular tuberculosis, one of intermuscular abscess) nine were caused by the human type of bacillus, two by the bovine type, and one by a type which resembled the bovine but differed slightly in cultural characteristics and virulence.

From sixty cases of scrofuloderma, fifty-two cultures of the tubercle bacilli were obtained. Of these, sixteen showed the bovine type of bacillus, four a type less virulent than the ordinary bovine bacillus, and thirty-two the common human type.

The author reports that in England 1,068 cases of tuberculosis have been examined for the type of tubercle bacillus, 803 showed the human type, 194 the bovine, and five a mixed type.

N. NOVICK⁴ has studied the incidence of bovine infection in tuberculous meningitis. He quotes Park and Krumwiede, who found 15 per cent. of bovine infection in tuberculous meningitis among 1,000 cases of all forms of tuberculosis, and Rosenau, who analyzed 1,040 cases of tuberculous meningitis, which included those of Park and Krumwiede. Rosenau's figures were as follows: Among 685 patients 16 years of age or over, with tuberculous meningitis, nine, or 1.3 per cent., showed the bovine type of bacillus; among 132 patients between 5 and 16 years of age, thirty-three, or 25 per cent., showed the bovine type; among 120 patients under 5 years of age, fifty-nine, or 49 per cent., showed the bovine type. The striking feature of these figures is the alarming percentage of the bovine infection in children under 5 years. Undoubtedly this is due to the facts that milk, which is the probable

3. Griffith, A. S.: The Bacteriologic Characteristics of Tubercle Bacilli from Different Kinds of Human Tuberculosis, *J. Path. & Bacteriol.* **23**:129 (Feb.) 1920.

4. Novick, N.: Incidence of Bovine Infection in Tuberculous Meningitis, *J. M. Research* **41**:239 (Jan.) 1920.

means of transmitting the tubercle bacillus, is the chief element in the diet of children and that the bovine bacillus is much more virulent in children.

The author's series consisted of forty-eight cases of tuberculous meningitis; two were in adults and forty-six were in children of from 4 months to 16 years. Forty-eight strains of tubercle bacilli were isolated from the cerebrospinal fluid in these cases and only three proved to be of the bovine type. One of the bovine strains was isolated from a case of meningitis in a baby 22 months old, one in a 6 year old child and one in a 16 year old patient.

SYMPTOMATOLOGY

J. V. COOKE and T. C. HEMPLEMANN⁵ believe that many children are infected with the tubercle bacillus and for a variable length of time harbor somewhere in their bodies a pathologically active tuberculous focus, which may be unsuspected. To this form is applied the term masked juvenile tuberculosis. The authors think that masked juvenile tuberculosis presents a sufficiently distinct clinical type to deserve a prominent place in the category of tuberculous affections in childhood. The clinical picture may be sketched as follows: A history of frequent coughs and colds with or without known exposure to tuberculosis; attacks of unexplained fever, often with afternoon elevations; anorexia; loss of weight, and asthenia. On examination there is found malnutrition, occasionally anemia, and signs in the chest referable to enlarged tracheobronchial nodes. In some instances there may be phlyctenular disease or skin tuberculids. The Pirquet or intracutaneous tuberculin test is positive and three-fourths of the children over 4 years of age give a positive complement fixation test for tuberculosis. The chest findings may be verified by the roentgen ray, which not infrequently reveals also unsuspected lesions of varying size and age in the lung parenchyma. The diagnosis must rest on a review of all findings, but the authors emphasize the value of the complement fixation test in calling attention to this class of cases. As to the fate of children with marked tuberculosis, three possibilities suggest themselves. By far the commonest is regression of the lesion with recovery, and the authors are of the opinion that these relatively harmless lesions may stimulate the body to produce certain protective substances against future infections. A second outcome is the development of a more manifest tuberculosis through extension of the process. And the third is the persistence of the marked lesions to adult life with a possible later development of active tuberculosis.

5. Cooke, J. V., and Hemplemann, T. C.: Masked Juvenile Tuberculosis, *Am. Rev. Tuberc.* 4:660 (Nov.) 1920.

Cooke and Hemplemann believe that the recognition of this marked form of tuberculosis is a matter of the greatest importance, because the inauguration of an antituberculosis regime results usually in a reasonably good chance of recovery.

P. ARMAND DE LILLE⁶ describes the evolution of tuberculosis in older children. If the infection is not a massive one, the onset is very insidious and the disease becomes manifest only after an infectious disease or an indoor winter life, which lowers the resistance and suppresses the formation of antibodies. There then develop fatigue, stationary weight or loss of weight, listlessness, anorexia, and usually an evening rise in temperature. The child, however, does not appear to be ill. After several weeks these symptoms disappear, but the Pirquet test, previously negative, is found to be positive. At this stage physical and roentgen-ray examination reveal enlarged glands in the tracheo-bronchial region. If the child's resistance is sufficient, the disease then remains latent until adult life, when the glands gradually diminish in size and sclerose. If, however, the resistance is not great enough to overcome the infection, the second stage of generalization, namely, a miliary tuberculosis, results. The clinical symptoms then depend on the degree of generalization. If widespread, there is high temperature, rapid pulse, emaciation, lassitude, without signs of localization, which last from ten to twenty days, when signs of pulmonary or meningeal involvement appear. If the tubercles are very discrete there may be prolonged fever without localized signs, the "typho-bacillose" of Landouzy; there may be only a single localization, as a pleuritis, peritonitis or joint effusion. Sometimes only a few tubercles are scattered in various organs, where they become sclerosed or resorbed or develop into local tuberculous foci.

NOBECOURT and PARAF⁷ believe that chronic pulmonary tuberculosis in children may have an acute rapid onset or a slow progressive one. In cases with an acute onset there are general symptoms, as fever, emaciation, weakness, anorexia; functional signs, as slight dyspnea, a dry cough, or a paroxysmal cough, like whooping cough. The physical signs depend on whether the lesion is a tracheobronchial adenopathy or a dry pleurisy located at the apex, in the fissures, or at the hilus.

Cases with a slow progressive course occur usually at puberty. The symptoms are those of an active tuberculosis, emaciation, fatigue, pallor, anorexia, digestive disturbances, tachycardia and arterial hypo-

6. Armand-de Lille, P.: Tuberculosis in Older Children, *Bull. méd. Par.* **34**:999 (Nov. 13) 1920.

7. Nobecourt and Paraf: Chronic Pulmonary Tuberculosis in Older Children, *Rev. de la Tuberc.* **1**:329, 1920.

tension. The physical signs are difficult to detect and to interpret. A normal resonance at the apex may be accompanied by a feeble or rough low pitched respiration. Feeble respirations are not characteristic and may be due to imperfect nasal breathing, tracheobronchial adenopathy, an old pleurisy, cardiac disease or an asymmetrical thorax. The first valuable signs at the apex are impaired resonance, increased resistance, prolonged expiration and exaggerated voice sounds. A prolonged blowing expiration is corroborative evidence. Enlarged tracheobronchial glands, however, can cause an atelectasis and congestion of the apex and can simulate a tuberculous process. The roentgen ray is an important aid in differentiation.

H. ELIASBERG and W. NEULAND⁸ have studied a condition found occasionally in the lungs of tuberculous children, which they term "epituberculous infiltration." Clinically, children with this condition are pale and emaciated; they cough, have no appetite, and frequently have a slight temperature. These symptoms come on gradually. Physical examination reveals a massive dulness of an entire lobe, usually one of the upper lobes, with bronchial breathing but no râles—findings out of all proportion to the slight general disturbance. The sputum does not contain tubercle bacilli; but all these patients show a positive Pirquet reaction. Often there are other evidences of tuberculosis, as fistulae, tuberculous glands or tuberculids. There is usually a family history of tuberculosis. The disease runs a benign course; the symptoms disappear and the infiltration is gradually absorbed, until in the course of months it has disappeared entirely. No evidences of contraction of the lung, as drawing in of the thorax, displacement of the heart or mediastinum, or bronchiectasis, accompany resolution.

The authors believe the condition to be a chronic, nonspecific infiltration, with a simultaneous tuberculous infection and that it must be differentiated from the gelatinous infiltration of Laennec, the chronic bronchopneumonias, which follow whooping cough and influenza, especially when accompanied with a pleural exudate, foreign bodies, stasis, open ductus botalli, and, in young children, a persistent thymus.

As the infiltration ultimately subsides, no treatment is necessary beyond measures to promote resolution and absorption.

A. WOLFF-EISNER⁹ believes that in tuberculous individuals exudative manifestations appear frequently and that there is a hypersensi-

8. Eliasberg, H. and Neuland, W.: Epituberculous Infiltration of the Lung in Children, *Jahrb. f. Kinderh.* **93**:88, 1920.

9. Wolff-Eisner, A.: The Relation between Tuberculous Infection and Constitutional Diathesis, *München med. Wchnschr.* **67**:93 (Jan. 23) 1920.

tiveness not only to the specific proteid of the tubercle bacillus but also to other proteids (nuclein, albumoses, etc.). In tuberculous children variations in the normal electrical reactions also occur frequently. He thinks manifestations of exudative diathesis and spasmophilia are due not only to nutritional disturbances and absorption of toxins from the intestine but also to the absorption of foreign proteids from any source, hence they are evidences of hypersensitiveness or anaphylaxis.

A. WOLFF-EISNER¹⁰ has made a further study of the nervous excitability in tuberculous children. He thinks that if there is any relation between tuberculosis and the exudative and spasmophilic diathesis the electrical reactions in these conditions should be analogous. The electrical reactions of fifty-two children suffering from osseous tuberculosis were taken. As they were all between 6 and 14 years of age, there were no signs of spasmophilia. The results were interesting. The electrical reactions varied from the normal but were not characteristic of those of the exudative and spasmophilic diatheses, in that the A.C.C. was greater or equal to the C.C.C. Nevertheless, Wolff-Eisner believes these results shows a relation between tuberculosis and the diatheses of childhood.

C. MUNIGURRIA¹¹ reports a case of cardiotuberculous cirrhosis in a 6 year old boy. When seen by him, the child had been ill one year with pain in the extremities, fever, general weakness, insomnia, and loss of appetite. On examination there was dulness over the right apex, with bronchial breathing, pain over the sterum and arrhythmia. While under observation, the child developed a general edema, icterus, cyanosis of the extremities and dyspnea, with dulness and râles over the right base. The heart dulness was increased. The liver was enlarged and painful; the spleen was palpable. Death occurred six months after the first examination. Necropsy showed biliary ascites, tuberculosis of the mesentery glands, fatty degeneration of the liver, miliary tuberculosis of the lungs, tuberculous pericarditis with the pericardium adherent to the pleura and diaphragm. A large tubercle was found at the opening of the right ventricle.

R. SIMONINI¹² reports an instance of tubercle of the myocardium in an 18 month old infant. The tumor was the size of a nut, located on the outer side of the right auricle. It penetrated into the myocardium but not into the auricle.

10. Wolff-Eisner, A.: Changes in the Electrical Excitability in Tuberculosis of Childhood, *Beitr. z. Klin. d. Tuberk.* **45**:283 (Nov. 25) 1920.

11. Munigurria, C.: Cardio-Tuberculous Cirrhosis, *Abstr. Zentralbl. f. d. ges. Kinderh.* **9**:577 (Nov.) 1920.

12. Simonini, R.: A Report of a Large Tubercle of the Heart in an Eighteen Month Old Infant, *Abstr. Jahrb. f. Kinderh.* **94**:67, 1921.

T. H. and H. O. GUNewardENE¹³ report a case of extensive primary tuberculosis of the heart in a 6 year old boy. The child died ten days after admission to the hospital. At necropsy both ventricles were hypertrophied and dilated. In the right ventricle, just above the attachment of the tricuspid valves, were two nodular masses about 1 c.mm. in diameter. Small isolated areas of firm, white tissue infiltrated the interauricular septum and the wall of the right auricle and the heart muscle at the root of the pulmonary vein. The visceral pericardium was completely adherent, but no tubercles could be seen. On section there was an indurated ulcer 1 cm. \times $1\frac{1}{2}$ cm. in diameter. bacilli. Tuberculous lesions were not found by the naked eye in any of the other organs. The authors regard this as a case of primary tuberculosis of the myocardium. They found forty-one cases of tuberculosis of the myocardium reported in the literature but only one with a similar location and no other in which the disease was primary in the myocardium.

Under the name of hyperplastic tuberculosis of the small intestine J. RANSOHOFF¹⁴ describes a tuberculous process, which because of its chronicity permits of excessive effort at repair and assumes the guise of a neoplasm. In most cases the disease involves the cecum and terminal coils of the ileum, and is the primary localization of the tuberculosis.

The author's patient was a 9 year old girl, who had previously been operated on for tuberculous glands. For two or three years the patient had complained of colicky pains, which occurred four or five times a day, soon after taking food but which had no relation to bowel movements. The pain was localized in a small area, immediately to the left and slightly below the umbilicus. Examination of the abdomen showed a mass about the size of an apple in this location. At operation a growth was found at the lower end of the jejunum, which involved about seven inches of the intestine. The lymph glands of the mesentery were enlarged. About ten inches of the intestine was resected and recovery was uneventful.

The tumor mass was found to consist entirely of the intestinal wall. On section there was an indurated ulcer 1 cm. \times $1\frac{1}{2}$ cm. in diameter. Microscopically, the tumor consisted of small round cells and polymorphonuclear cells; rarely a multinucleated giant cell occurred. In spite of the resemblance to a sarcoma, the author believes the growth to be tuberculous because of the history and the presence of the ulcer.

13. Gunewardene, T. H. and Gunewardene, H. A.: Extensive Primary Tuberculous Disease of the Heart, *Proc. Roy. Soc. Med. Lond. Sec. Dis. Child.* **13**:38 (March) 1920.

14. Ransohoff, J.: Hyperplastic Tuberculosis of the Small Intestine, *Ann. Surg.* **72**:196 (Aug.) 1920.

He considered, however, the possibility of a sarcomatous growth in primary tuberculous tissue.

J. H. M. KNOX¹⁵ reports a case of tuberculoma of the midbrain associated with tuberculous meningitis. The patient was a colored boy 3 years of age, who was taken to the hospital because of general weakness, trembling and drooping of the eyelids. The patient had appeared to be perfectly normal until six months before, when he stopped crying almost completely. Four months later it was noted that his hands shook when he fed himself. About the same time his eyes began to droop. On examination his general condition seemed excellent. The eyes showed the following: The pupils reacted to light, the left better than the right. There was a marked bilateral ptosis of the eyelids and a definite lateral deviation of the eyeballs to the right, also an occasional lateral nystagmus of the right eye. The child was sent home but returned for admission two weeks later, when a distinct paraplegia of both lower extremities was noted. The spinal fluid, obtained under a marked increase in pressure, gave a reaction for globulin, and contained an increased number of cells of the mononuclear type. The roentgen-ray examination of the head showed a moderate internal hydrocephalus and a probable tumor above the sella turcica. The Pirquet test was frankly positive. Ten days after admission a slight rigidity of the neck was noticed and from this time on the child grew constantly weaker. Drowsiness gradually deepened, general convulsions developed, and the boy died forty-two days after the first observation.

The acquired ptosis, the tremor of long standing, and the gradually developing external strabismus led Knox to venture the diagnosis of tumor of the midbrain interfering with the nuclei of the third and fourth cranial nerves. The positive Pirquet reaction and development of a meningitis toward the end suggested that the tumor was of tuberculous nature. This diagnosis was confirmed at necropsy when a solitary tubercle of midbrain and of the right parietal lobe, and a tuberculous meningitis were found.

H. KOCH¹⁶ is of the opinion that occasionally recovery takes place in cases of brain tubercle. He draws this conclusion from the study of three cases and from the review of the literature on the subject. His first case was a 5 year old girl who entered the hospital because of vomiting, ataxic gait and a positive Romberg's sign. While under observation there developed a marked tremor. The Pirquet reaction

15. Knox, J. H. M.: Lesions in the Midbrain, *Am. J. Dis. Child.* **20**:436 (Nov.) 1920.

16. Koch, H.: Contribution to the Etiology of Brain Tubercle, *Ztschr. f. Kinderh.* **24**:197 (Dec.) 1919.

was positive. The child remained in the hospital four months; on discharge all symptoms had disappeared, except the positive Romberg. The second case was that of a 9 year old child, who had for eight weeks attacks of dizziness and vomiting. Fourteen days before entering the hospital she became unconscious and developed a left sided paralysis. On entrance there was ataxic gait, a positive Romberg's sign, a paralysis of the left abducens nerve, and hyperesthesia of the left cornea. After seven months' observation the gait became normal and the child was discharged with no evidence of her illness, except the paralysis of the abducens nerve.

The third case was a 5 year old child, who was admitted to the hospital because of convulsions and muscular twitchings. The child was under observation for eleven months and the diagnosis of brain tubercle was based on the presence of irritative symptoms and a positive tuberculin test. At first the child showed no improvement and during an attack of measles had as many as twenty-three convulsions a day. Two weeks after the onset of the measles the convulsions subsided but recurred with greater severity about the fourth week. This period lasted fourteen days, when the convulsions ceased altogether. The author thinks that during the attack of measles there was a formation of miliary tubercles around the tuberculoma (he has seen this at necropsies) which caused the exacerbation of the convulsions. Their cessation was due to relief of pressure on nerves or blood vessels by absorption of inflammatory products or to the opening of the cerebro-spinal canal, which could have been obstructed by the inflammatory products.

Koch discusses the possibility of permanent cure and cites a few instances reported in the literature. Nevertheless, he believes the prognosis is usually unfavorable, chiefly because the tubercle is a metastatic tuberculous process and the prognosis depends upon the extent of the original disease and because, too, there is a tendency for patients with brain tubercles to develop tuberculous meningitis.

A. WAGNER¹⁷ reports a case of solitary tubercle of the spinal medulla in a 14 year old boy. For three weeks before entering the hospital he had complained of severe pain in the lumbar region and right leg, vomiting and headache. Examination on entrance showed marked pallor and emaciation, with tuberculous lesions on the lower extremities. There was tenderness over the spine and edema in the lumbar region. The Pirquet test was positive. The muscles of the right leg, especially those of the thigh and buttocks, were atrophic and paralyzed. There was a positive Babinski and Kernig's sign. Lumbar

17. Wagner, A.: Contribution to the Diagnosis of Solitary Tubercle of the Spinal Cord, *Ztschr. f. Kinderh.* **25**:322 (June) 1920.

puncture gave a slightly turbid fluid under pressure, with a positive Nonne and 240 cells to the cubic centimeter, only 8 per cent. of which were neutrophils, the remainder being polymorphnuclear cells. The clinical diagnosis was solitary tubercle of the brain; tuberculous meningitis; tuberculosis of the skin. The cause of the paralysis of the leg was undecided. The child died and necropsy showed old caseous tuberculosis of the bronchial glands, pulmonary tuberculosis, miliary tubercles of spleen, liver, and kidneys, multiple conglomerate tubercles in the brain, chronic internal hydrocephalus, and tuberculous ulcers in the colon. In the lumbar region of the cord was a cherry sized tubercle, which accounted for the paralysis of the right leg.

According to the writer, solitary tubercles of the spinal cord are rare. The disease usually begins with weakness, pain and paresthesias in the extremities; later there is a disturbance in temperature sense. Muscular atrophy and paralysis occur early. Compression myelitis and spinal syphilis are to be considered in differential diagnosis. Remissions and exacerbations of symptoms and the roentgen-ray finding of spinal caries speak for compression myelitis and a positive Wassermann reaction for syphilis.

SCHMINCKE¹⁸ reports a case of solitary tubercle in the cervical cord. The patient was an 8 month old child who for three months had lost weight and had cried continuously. The child did not attempt to sit up or to use the right arm. There was also less power in the right than in the left leg. While under observation, the child became apathetic and developed stiffness of the neck and general convulsions.

At necropsy there was found a disseminated caseous tuberculosis of the left upper lobe, caseous tuberculosis of the bifurcation and hilus glands, miliary tuberculosis of the liver, spleen and kidneys, tuberculous basilar meningitis. In the region of the cervical enlargement of the spinal cord the dura was adherent to the pia. The cervical enlargement was greater than normal, and on cross section there was found a caseous area, the size of a pea.

A. GENDRON¹⁹ reports three cases of erythema nodosum and one of a miliary eruption in children of a tuberculous family. The disease had a period of incubation of four days, in all of them, a period of invasion with the usual phenomena of infection, and a period of eruption of twelve days, followed by complete cure. Four months later one of the children developed a pleurisy. In one the roentgen ray showed an opaque zone near the fissure in the left lung and the other two children gave positive tuberculin reactions. These facts cause

18. Schmincke: A Case of Solitary Tubercle in the Cervical Cord, *Jahrb. f. Kinderh.* **92**:407, 1920.

19. Gendron, A.: Erythema Nodosum and Tuberculosis, *Bull. et mém. Soc. méd. d. hôp. de Par.* **44**:475 (March 26) 1920.

the writer to believe that the four children were already affected with tuberculosis, when they became ill with the erythema. He is of the opinion that tuberculosis creates a favorable ground for the development of erythema nodosum.

L. LAEDERICH and C. RICHEL²⁰ discuss the relation of erythema nodosum to tuberculosis. They believe clinical, biologic and bacteriologic studies point to a close connection between the two conditions. As regards clinical facts, erythema nodosum has often been observed in patients with open tuberculosis. It has appeared in persons apparently well but who soon after the attack develop signs of an acute tuberculosis; and it has appeared simultaneously with other manifestations of acute or subacute tuberculosis.

Biologic studies are very suggestive. Patients with erythema nodosum almost invariably give a positive tuberculin test. Injection of these patients with tuberculin causes the appearance of a nodule of erythema nodosum. Also often in tuberculous patients an intradermal injection of tuberculin will cause the appearance of the large red nodules of erythema nodosum.

In experimental animals the bacillus of Koch has been found in the blood during an attack of erythema nodosum and a number of observers have reported finding this organism in the lesions. Although the writers do not think that all cases of erythema nodosum are of tuberculous origin, they conclude from the facts they observed that tuberculosis is an important factor in the etiology.

E. WARD²¹ is of the opinion that erythema nodosum is a toxic manifestation of many different conditions, one of which is tuberculosis. That the occurrence of erythema nodosum and tuberculosis is not merely a coincidence is proved by the fact that erythema nodosum has been known to occur after an injection of tuberculin. The author has noticed the appearance of erythema in tuberculous patients, when a chronic condition becomes more acute and when the symptoms of tuberculosis first become noticeable in a patient under observation as a contact.

T. MCCRIRICK²² reports a case of tuberculosis verrucosa cutis of the foot in a 12 year old boy. The lesions were of four years standing and consisted of a warty growth, which involved the greater part of the thin skin of the sole and inner side of the foot. The height of the growth above the general skin level was three millimeters. The

20. Laederich, L. and Richet, C.: Erythema Nodosum and Tuberculosis, *Rev. de la Tuberc.* **1**:229, 1920.

21. Ward, E.: Erythema Nodosum and Tuberculosis, *Brit. M. J.* **2**:811 (Dec. 20) 1919.

22. McCririck, T.: Tuberculosis Verrucosa Cutis of the Foot, *Brit. J. Child. Dis.* **17**:26 (Jan.-March) 1920.

source of infection was evidently a sister, who had at the time of appearance of the lesions multiple tuberculous abscesses. The child ran about barefoot in warm weather and a cut or scratch evidently became inoculated from carelessly handled dressings.

C. WITH²³ observed an atypical tuberculous eruption, which appeared on the extremities of a 7 year old child, being treated for lupus. On the extensor surface of the upper and lower extremities was a bright red eruption, consisting of lentil sized papules, slightly infiltrated and with central scaling. There was a diffuse scaly infiltration of the skin surrounding the lesions.

D. GUTHRIE²⁴ found thirteen cases of tuberculous origin among seventy-nine cases of chronic otitis media, in which the cause had been noted. All cases, except one, occurred in infants 1 year of age. The disease was characterized by a painless, insidious onset. The discharge was frequently the first sign of the disease. Facial paralysis was noted in seven cases and enlarged parotid glands in all. The author believes that these cases are due to milk infection and that the infection is carried to the middle ear by way of the eustachian tube.

B. S. VEEDER and T. C. HEMPELMANN²⁵ subjected 196 children with phlyctenular disease to a careful study to determine the possible presence or absence of tuberculous infection. The study revealed an intimate association of the two diseases. Skin tuberculin tests were positive in more than 92 per cent. of the cases. The results of the complement fixation test for tuberculosis were strikingly similar to those obtained in cases of proved tuberculosis. Tuberculous lesions involving other organs than the eye were definitely demonstrable in more than half the cases. Cough, malnutrition and history of exposure to other cases of tuberculosis were frequent.

TUBERCULOSIS OF THE TRACHEOBRONCHIAL AND MESENTERIC LYMPH NODES

M. NOBECOURT²⁶ recounts the symptoms of tracheobronchial adenopathy. Respiratory disturbances are in proportion to the size of the glands. Dyspnea and shortness of breath are frequent. The dyspnea is more marked on exertion and in severe cases accompanied with expiratory difficulty in children under 3 years of age, and inspira-

23. With, C.: Atypical Tuberculid on the Arm of a Seven Year Old Child, *Abstr. Zentralbl. f. d. ges. Kinderh.* **10**:221 (Feb. 8) 1921.

24. Guthrie, D.: Thirteen Cases of Aural Tuberculosis in Infants, *J. Laryngol. Rhinol. & Otol.* **35**:99 (April) 1920.

25. Veeder, B. S. and Hemplemann, T. C.: Phlyctenular Ophthalmia and its Relation to Tuberculosis, *Arch. Pediat.* **37**:396 (July) 1920.

26. Nobecourt, M.: Tracheobronchial Adenopathy, *Progrès méd.* **35**:216 (May 15) 1920.

tory in children above 3 years. Two types of dyspnea are associated with enlarged bronchial glands, asthmatic attacks which come on suddenly, sometimes during the night, sometimes during the day, with difficulty in inspiration but quiet blowing expiration and spasm of the glottis which is accompanied by a rough noisy respiration. Aphonia and dysphonia due to paralysis of the recurrent laryngeal nerve may also occur—as may palpitation and difficulty in swallowing.

Enlarged tracheobronchial glands give rise to characteristic physical signs; dilated veins on the chest, but the glands must be very voluminous to cause this phenomenon; feeble expansion on one side of the chest; dulness and bronchial breathing in the intercostal and vertebral zones and D'Espine's sign. Evidences of passive congestion, such as diminished resonance and râles, are frequently found at the right base. In some children enlarged bronchial glands are accompanied by attacks of bronchitis, in others by a very obstinate bronchitis or bronchopneumonia. In these instances signs of pulmonary tuberculosis are found associated with those of tracheobronchial adenopathy. Radioscopy gives precise information of the pulmonary conditions.

Nobecourt calls attention to the fact that enlarged bronchial glands are not always due to tuberculosis. They may occur in the course of a bronchopneumonia, bronchitis or whooping cough. They are frequently associated with adenoid vegetations and are found in cases of hereditary syphilis and leukemia.

V. OHLEN,²⁷ discussing the early diagnosis of hilus gland tuberculosis, bases his conclusion on the study of seventy-seven children. He lays special stress on a failure to develop physically, the tuberculin reaction, and the roentgenogram. He thinks the most important of these is the failure to make satisfactory gain in development, associated with which is a condition of poor nutrition and a marked pallor of the skin and mucous membranes. Night sweats and general weakness and cough are concomitant symptoms. The cough is usually the symptom which causes the parent to consult a physician.

V. Ohlen frequently used the Ponndorf tuberculin test, instead of the Pirquet. Four or five vaccination scratches, from 5 to 6 cm. long, are made near one another on the upper arm. These are intersected by three or four cross lines, so as to make a lattice work. Two drops of pure tuberculin are well rubbed into the scarification. Observations are made after forty-eight hours. By this method a larger amount of antigen comes in contact with the scarified area than with the Pirquet test.

The author thinks that in only occasional cases can a positive diagnosis be made by the roentgen ray alone and this is when sharply

27. v. Ohlen: Early Diagnosis of Hilus Gland Tuberculosis, *Beitr. z. Klin. d. Tuberk.* 45:343 (Nov. 25) 1920.

defined hilus shadows are present. Repeated plates must be made at intervals, in order to draw correct conclusions. It is a valuable experience to see, on the one hand, how in the course of months hilus shadows become thicker, narrow streaks stretch out into the lungs, and new isolated shadows appear; or, on the other hand, to see how the hilus shadow becomes smaller, the cardiac outline clearer and the cardiophrenic angle becomes again visible. In all except one of the author's cases, in which the tuberculin test was positive, were there positive roentgenologic changes in the hilus region. Moreover, the intensity of the reaction was parallel with the severity of these changes.

K. KLARE²⁸ believes that D'Espine's sign is most valuable to establish the diagnosis of bronchial gland tuberculosis in children. Again and again he has proved its worth under control of the roentgen ray.

H. MERY²⁹ believes that the early diagnosis of tuberculous bronchial glands is the most important factor in the battle against tuberculosis in childhood.

A family history of tuberculosis and a previous history in the child of pleurisy, cervical adenitis, frequent attacks of bronchitis, a slow recovery from whooping cough or measles are important presumptive evidence of tuberculous bronchial glands. In examining the child attention is first called to emaciation, pallor, development of hairy growth, presence of cervical, axillary, and inguinal glands. Of the functional symptoms the paroxysmal cough, like whooping-cough, is the most important. Examination of the chest shows enlarged veins. Percussion of the anterior portion of the chest is more important than of the posterior. Here there is dullness and a resistance which extends two fingers' breadth to the right and left of the sternum. Dullness in the paravertebral area is important, as are modifications of respiratory and increased transmission of voice sounds. The author thinks a feeble respiratory murmur in this region is of important diagnostic significance. Rough breathing is frequently found over the bases, and crepitant râles due to transient pulmonary congestion. The roentgen ray should be used to complete the examination.

H. MERY and L. GIRARD³⁰ describe active forms of hilus tuberculosis in children. The active process may be confined to the glands or may involve the periglandular structure. If confined to the glands, there are more physical findings anteriorly than posteriorly. There is

28. Klare, K.: Spinal Auscultation in the Diagnosis of Enlarged Bronchial Glands, *Ztschr. f. Kinderh.* **27**:169 (Dec. 16) 1920.

29. Mery, H.: Early Diagnosis of Bronchial Gland Tuberculosis, *Presse méd.* **28**:873 (Dec. 4) 1920.

30. Mery, H., and Girard, L.: Active Forms of Hilus Gland Tuberculosis in Childhood, *Rev. d. la Tuberc.* **1**:289, 1920.

parasternal dulness in the two first intercostal spaces and a rough respiratory murmur. The dulness may be so marked that an apical or interlobar pleurisy or a hydatid cyst is suspected. The roentgen ray shows that the apices are clear, but there is present a paracardiac triangular shadow, with the base toward the heart.

If there is periglandular involvement besides the signs described, subcrepitant râles are heard posteriorly in the paravertebral spaces. General symptoms, such as fever, emaciation, loss of appetite, are also present. An interlobular pleuritis usually occurs and is manifested by severe pain. On the roentgenogram the interlobular pleuritis gives a transverse shadow which extends from the hilus to the axilla, with the base toward the heart and the apex toward the axilla.

W. PFEIFFER³¹ adds a contribution to the value of direct tracheobronchoscopy in stenosis of the respiratory system from tuberculous bronchial glands. He believes that this procedure is not only of value in confirming the diagnosis of enlarged bronchial glands but has also a therapeutic worth. Broken-down bronchial glands can rupture into the air passages and cause suffocative attacks or death from suffocation. Before rupture of the gland the bronchoscope shows in nearly every instance a bulging, redness and swelling of the mucous membrane, which has a smooth satin-like appearance. Widening and flattening of the carina of the trachea is usually a sign of enlargement of the inferior tracheobronchial glands. The right side of the trachea and the right bronchus are more often affected than the left. In case of rupture the point of perforation can usually be demonstrated and cheesy or purulent masses are found in the air passages. The cheesy masses look yellowish-white or chalky and frequently have a very foul odor. They can be removed by suction, with absorbent cotton pledgets or foreign body forceps. Sometimes they are coughed up through the bronchoscope during the operation. Sometimes the pressure of the tube in the neighborhood of the perforation causes cheesy masses to be evacuated into the air passages. Granulation tissue frequently forms on the edges of the perforation after the gland has ruptured. Rupture usually takes place slowly. Portions of the gland, passing through the small opening, cause cough and suffocative attacks, like those caused by small foreign bodies which do not entirely obstruct the air passages. The cough is paroxysmal and accompanied by a spasm of the larynx. This is followed by a latent stage in which there are no symptoms. Gradually, however, usually in consequence of a severe coughing attack, the perforation becomes larger and the broken-down gland is protruded into the air passages, producing all degrees of

31. Pfeiffer, W.: Value of Direct Tracheobronchoscopy in Stenosis of the Respiratory System from Tuberculous Bronchial Glands, *Beitr. z. Klin. d. Tuberk.* **41**:197, 1919.

dyspnea—even to complete suffocation. Rupture of the gland into the air passages sometimes causes a subcutaneous emphysema, which spreads rapidly over the neck and thorax.

As to the treatment of tuberculous bronchial glands, if there are no symptoms of pressure, hygienic measures can be resorted to and many patients are cured permanently. If, however, there are symptoms of pressure, the patient should be taken to a hospital, where he can be under observation and examined with the bronchoscope. In children under 5, because of danger of subglottic swelling from pressure of the tube, a tracheotomy should first be performed. Tracheotomy alone is insufficient to prevent death from suffocation, in case the gland has already ruptured, though occasionally the obstructing gland is coughed up through the tracheotomy wound. By means of the bronchoscope the point of obstruction is located, the mucous membrane over the protruding gland opened, and the caseated masses removed. The operation must be performed repeatedly because of the gradual breaking down of the gland.

As asserted by H. M. CHUTE,³² mesenteric lymph nodes react to infection in a manner similar to lymph nodes in other situations. In children and adults enlarged mesenteric glands are one of the causes of abdominal pain, which gives no hint as to its origin until exploratory laparotomy is performed. In children the early history of the condition is characterized by vagueness. The child is anaemic and listless and suffers from loss of weight and appetite. Digestive disturbances, like diarrhea or constipation, are common. As the inflammatory process progresses, there occur attacks of abdominal pain, which shift about, probably because of the ease with which the nodes move within the mesentery. Fever and vomiting and moderate rigidity over the muscles may occur. If, as is frequently the case, the ileocecal glands are involved, the picture may be one of acute appendicitis. As the disease advances to abscess formation, the symptoms are more definite and localized. A tender mass is found in the abdomen with moderate muscle spasm. If rupture takes place, there are symptoms of generalized peritonitis. Mesenteric glands of long standing may become calcified, when a roentgen-ray examination may lead to an incorrect diagnosis of renal or ureteral stone. Enlarged mesenteric glands may cause intestinal obstruction from adhesion of the gut or omentum to a gland.

Chute emphasizes that in children recurrent attacks of abdominal pain with fever, little or no vomiting, constipation and loss of weight, should remind one of the possibility of tuberculous mesenteric glands.

32. Chute, H. M.: Enlarged Mesenteric Glands, Boston M. & S. J. **183**:409 (Sept. 30) 1920.

The diagnosis can sometimes be confirmed by combined rectal and abdominal palpation.

Treatment is surgical, followed by hygienic measures, and the prognosis is good.

E. GEHRELS³³ classifies as mesenteric tuberculosis only those cases in which the mesenteric glands alone are affected and omits all in which there are also intestinal or peritoneal lesions. He believes the tubercle bacillus can pass through the intestinal wall without causing specific changes. The bovine is the more common type of organism found. The disease is not frequent and in the author's experience was found in only 1 per cent. of 15,000 autopsies. Two thirds of the cases occurred in children. The writer discusses two forms, the acute and chronic. The acute form may be easily mistaken for other acute abdominal disturbances. In the chronic form there are recurring attacks of abdominal pain, usually located in the ileo-caecal region and associated with loss of weight and fever. Functional disturbances, like spastic constipation or diarrhoea, may occur. Intestinal obstruction and peritonitis are the most important complications. The diagnosis is difficult. The palpation of enlarged glands, the temperature curve, and the roentgen ray are aids. The lack of abdominal distention and sensitiveness to pressure help to differentiate the disease from appendicitis, which it resembles in the earlier manifestations. Tuberculosis of the mesenteric glands is more amenable to treatment than any other form of tuberculosis. Forced feeding, change of climate, artificial heliotherapy, deep abdominal roentgenotherapy, and tuberculin injections are all valuable procedures. Surgical intervention is indicated only when long continued internal treatment has failed.

DIAGNOSIS

P. GROSSER³⁴ emphasizes the following points in the diagnosis of early tuberculosis in children. Very important is an exact history of possible exposure to the disease. The temperature curve needs careful study. Irregular, often intermittent temperatures which last over a long period of time are suspicious. It must not be forgotten, however, that similar temperature curves occur in children with infections of the upper respiratory tract and in nervous children. Night sweats are not frequent in early tuberculosis. The involvement of three groups of glands is suggestive, namely: those at the angle of the jaw, those just above the clavicle, and the thoracic glands. Early involvement of the tracheobronchial glands is difficult to detect and the glands must

33. Gehrels, E.: Tuberculosis of the Mesenteric Glands, *Deutsch. med. Wchnschr.* **45**:44 (Oct. 9) 1919.

34. Grosser, P.: Diagnosis of Tuberculosis in Children, *Deutsch. med. Wchnschr.* **46**:369 (April 8) 1920.

be of considerable size before they cause symptoms of stasis or pressure or before signs can be obtained by percussion. Enlarged veins on the chest frequently occur in normal children and are of no diagnostic value. Pressure on the sympathetic nerve gives rise to inequality of the pupils. Eustace Smith's sign is of little value. More important is an expiratory crow and the cough which resembles whooping cough. Direct percussion over the vertebra gives no information; but D'Espine's sign is very important. The roentgen ray is a great aid in diagnosis, but interpretation of the plates is difficult and a diagnosis of tuberculosis must be made only in conjunction with other findings. A negative Pirquet test, except in infants during the period of incubation, in cachectic conditions, and during the febrile stage of acute infections, means the absence of tuberculous infection. A positive Pirquet reaction indicates a tuberculous infection but not tuberculous disease.

G. MIOCHE³⁵ has studied the diagnostic value of the Pirquet reaction, the frequency of positive reactions, and the mortality rate of children who react to the test. She affirms that a positive tuberculin reaction always indicates a previous infection with the tubercle bacillus and that there seems little doubt that the bacilli active or latent are still present. Necropsies on individuals who gave a positive reaction always show tuberculous lesions. Except in acute infections, rapidly progressive tuberculous disease, and advanced cachexia, a cutaneous test, negative on repeated examinations, always eliminates a diagnosis of tuberculosis. This has been proved either by the absence of tuberculous lesions at autopsy or by the clinical course of the disease.

O. K. KLERCKER³⁶ attempted by means of intracutaneous tuberculin tests to differentiate active and inactive tuberculosis. He gave 257 children the intracutaneous test using 0.01, 0.10 and 1.00 mg. tuberculin. The children were divided into three groups: (1) Those with clinical tuberculosis, forty children; (2) those with a suspicious tuberculosis, forty-six children, and (3) those, who after long observations were found free from tuberculosis, 171 children. In the first group, 52.5 per cent. reacted to 0.01 mg. and 30 per cent. to 0.10 mg., a total of 82.5 per cent. Five per cent. of the children gave no reaction even to 1.00 mg. Of these last, one was a case of miliary tuberculosis; the other was a case of peritonitis. Klercker believes that an active tuberculosis, except the very severe forms, will give a reaction to 0.1 mg. and in most instances to .01 mg. of tuberculin. Further clinical study of the cases showed that when a pulmonary tuberculosis is

35. Mioche, G.: *The Skin Tuberculin Reaction in Children*, Le Nourrisson 8:42 (Jan.) 1920.

36. Klercker, O. K.: *The Local Tuberculin Test in the Diagnosis of Tuberculosis of Childhood*, Abstr. Zentralbl. f. d. ges. Kinderh. 19:523, 1920.

present, a sensitiveness to less than 0.01 mg. tuberculin indicates a weakening of the defense against the infection, and a sensitiveness to less than 0.1 mg. indicates a hopeless outlook.

In the children of the second group a positive reaction to 0.01 mg. tuberculin was regarded as evidence of active tuberculosis, to 1.00 mg. as evidence of latent tuberculosis, and a positive reaction to 0.1 mg., if the children were not in very poor general condition, a healed tuberculosis.

In Group 3, 26 per cent. reacted to the tuberculin, 10 per cent. of these reacting to the smallest dose; and the writer believes that, in spite of no clinical evidences, this also indicates a healed tuberculosis.

From observations on three infants and a careful study of the literature R. DEBRÉ and P. JACQUET³⁷ have come to the following conclusions regarding the length of time after infection that the tuberculin test becomes positive and the presence or absence of symptoms during this period. After infection with the tubercle bacillus the time when the tuberculin test may be positive varies. The minimum time is six days; the maximum, four months. Variations in this period are due to the age of the patient, the quantity of the infecting material, and whether the cutaneous or intradermal test is used. The period is shorter in new-born than in older children, when the infection is a massive one and when the intradermal test is used. Except in new-born infants, no symptoms occur during this period.

PEYRER³⁸ reports a case in which the exact time between exposure to tuberculosis and the appearance of a positive intracutaneous reaction was determined. Because of a tuberculosis in the mother and the presence of dullness and bronchial breathing over the left lung in a 7 year old child was thought to have tuberculosis and was placed in a room with another child who had active tuberculosis. He remained there only thirty-six hours. On admission to the hospital the intracutaneous test with 0.001 mg. tuberculin was negative. The test was repeated daily with increasing doses and on the eighth day the child gave a positive reaction with 10 mg.

Peyrer quotes Hamburger, who believes that after infection with 0.5 mg. of bacilli the primary lesion appears in six days; with 0.00001 mg., it appears in twenty-five days. According to Peyrer, a Pirquet test is positive in from six to nine weeks after infection and an intracutaneous test is positive in three weeks. Peyrer says that infection can take place at the distance of one meter and in a very short

37. Debré, R. and Jacquet, P.: The Onset of Tuberculous Infection, *Ann. de méd.* 7:122, 1920.

38. Peyrer: Contribution to Tuberculous Infection, *Wien. med. Wchnschr.* 33:488 (June 3) 1920.

association; hence, a child should never be in the room with a patient whose sputum contains tubercle bacilli.

W. UNVERRICHT³⁹ reports a case which shows the greater sensitiveness of the intradermal over the Pirquet test. Two boys, 5 and 6½ years of age, respectively, occupied for twenty-four hours a room with an individual who had open tuberculosis. One boy who sat on the patient's bed gave a positive intracutaneous test with 0.1 mg. old tuberculin forty-five days after exposure. Seventeen days later the Pirquet test became positive. In the other boy who avoided the tuberculosis patient both tests remained negative. Unverricht believes the greater sensitiveness of the intracutaneous test is due to the larger area in which the tuberculin and tissues react and the more rapid absorption of the tuberculin in consequence of the greater pressure with which it is forced into the lymphatics.

As the bovine tubercle bacillus is found more frequently in tuberculosis of children than in that of adults, BERNHEIM-KARRER⁴⁰ believes it advisable to use the bovine tuberculin as well as old tuberculin in making the cutaneous test. But it must not be forgotten that because of the close relation between the two forms of tubercle bacilli, patients known to be suffering with tuberculosis of the bovine bacillus type will react to human tuberculin, and that bovine tuberculin produces non-specific reactions difficult to diagnose from true reactions. In 143 cases of tuberculosis positive results were obtained with human and bovine tuberculin. In eighty-four of these there was no difference between the reactions obtained. In fifty-nine the papule with one tuberculin was decidedly larger than that obtained with the other; or a positive result was obtained with only one form of tuberculin. In eight cases the reaction to old tuberculin was so slight that without the marked reaction obtained with the bovine tuberculin a diagnosis could not have been made. In seven cases there was a reaction only to human and in three cases only to bovine tuberculin. Thus in eleven cases, or 7 per cent., the bovine tuberculin was of greater value than the human tuberculin.

I. SYNWOLDT⁴¹ tested eighty children from 3 to 10 years of age with bovine and human tuberculin. Thirty-nine children had a history of exposure to tuberculosis but no physical findings; thirty-four had a more or less widespread pulmonary involvement; seven had tuberculous peritonitis or scrofula. Seventy-six per cent. of the children in the first

39. Unverricht, W.: Tuberculous Infection, Berl. klin. Wchnschr. **57**:1019, 1920.

40. Bernheim-Karrer: The v. Pirquet Tuberculin Reaction with Bovine and Old Tuberculin, Schweiz. med. Wchnschr. **50**:10 (Jan. 1) 1920.

41. Synwoldt, I.: The Diagnostic and Prognostic Significance of the Cutaneous Reaction with Bovine Tuberculin, Deutsch. med. Wchnschr. **46**:455 (April 22) 1920.

group gave a negative reaction to both tuberculin; 5.2 per cent. gave a positive reaction to both tuberculin, and 17.95 per cent. reacted only to the bovine tuberculin. In the second group, 14.7 per cent. gave a positive reaction to both tuberculin; 29.2 per cent. gave a negative reaction to both tuberculin; 2.9 per cent. gave a positive reaction to the human and a negative reaction to the bovine tuberculin; and 52.94 per cent. gave a negative reaction to the human and a positive reaction to the bovine tuberculin. The third group is too small for any conclusion to be drawn from the results but the high percentage of positive (42.86) reactions with the bovine tuberculin is significant. The author does not believe it possible to differentiate the type of infection by vaccination with both tuberculin but the human organisms seem more sensitive to the bovine tuberculin, so the test is a practical aid in the diagnosis of a tuberculosis, before it can be detected by physical findings. Synwoldt also regards a positive reaction to the bovine tuberculin as a favorable prognostic sign.

E. BJORN HANSEN ⁴² performed the Pirquet test on the inhabitants of an isolated parish in Norway, in which there had never been a death from tuberculosis. The total population was sixty and fifty-three were examined. The parish has its own school and very rarely do the people come in contact with the outer world. Twenty-one, or 40 per cent., showed a positive, and thirty-two, or 60 per cent., a negative reaction. No one below 16 years of age gave a positive reaction. A road connecting the parish with the outer world is being built and the author thinks it will not be long before the children will show a positive Pirquet reaction.

F. HAMBURGER ⁴³ has noticed that the sensitiveness to tuberculin varies at different seasons of the year. In his experience reactions were decidedly more marked in the Spring. In the Fall children suspicious of being tuberculous rarely gave a positive percutaneous or cutaneous test and the intracutaneous test was only positive with large doses of tuberculin. Children with healed lesions gave a late reaction with 1.0 mg. tuberculin.

Times of increased sensitiveness to tuberculin seem to run parallel to those of increased frequency of tuberculosis. The author offers no explanation of this variation in sensitiveness to tuberculin.

O. LADE ⁴⁴ has made a study of the microscopic changes in the skin after an intercutaneous tuberculin injection. His method of procedure

42. Hansen, E. Bjorn: v. Pirquet Investigation in a Parish without a Notified Death from Tuberculosis, *Tubercle* **1**:359 (May) 1920.

43. Hamburger, F.: Variations in Sensitiveness to Tuberculin at Different Times of the Year, *München. med. Wchnschr.* **67**:398 (April 2) 1920.

44. Lade, O.: The Capillary Microscopic Picture of the Intracutaneous Tuberculin Reaction, *Arch. f. Kinderh.* **68**:58 (Aug.) 1920.

was as follows: A dilution of 1:1000 or 1:100 of old tuberculin was injected through a very fine needle into the upper layer of the skin. Sufficient tuberculin was used to make a wheal 2 to 3 mm. in diameter. The skin was then made transparent by liquid petrolatum and magnified thirty-five times by means of a Zeiss microscope with a No. 3 objective and a No. 2 eyepiece. Direct sunlight was used for illumination. Directly after injection, when the white wheal is still present, there is seen microscopically a pale area in which the finer skin furrows disappear and the larger ones become narrowed to fine lines. The point of injection appears as a red canal at the end of which is a small amount of blood. A half hour after the injection, when the wheal has entirely disappeared, the skin furrows also have entirely disappeared, but the blood vessels are again plainly visible. After two and a half hours the furrows are again seen and after four hours the skin appears to be normal, except for a slight redness along the site of the injection. Six hours after the injection the redness again becomes intense and the furrows and the outlines of the blood vessels become less and less plain, as this redness increases. Twelve hours after injection well filled blood vessels are seen at the edge of the lesion, where the skin is paler. From eighteen to twenty-four hours after the injection, when a positive reaction can be determined microscopically, all the structures of the skin are blotted out by the diffuse inflammatory redness. The picture then remains stationary for from one to one and a half days, when the redness begins to fade and the blood vessels are again seen at the edges of the lesions. In the center, dark hemorrhagic points appear in the red background. These are the ends of the loops in the papillary bodies of the skin. The vessels of the subcapillary network become more marked than is normal and the skin furrows again become visible. On the third and fourth day the entire process has retrograded and there is a beginning scaling of the horny upper layers of the epithelium. The retrograde process lasts days or weeks, and if the reaction is observed at the end of the third week, besides the scaling there are found present in the horny layers of the epithelium homogeneous transparent masses, which can be lifted out with the point of a needle.

The changes which occur in the first half hour are not specific of tuberculin injections but are produced by injection of physiologic solution of sodium chlorid also; those which occur later, however, are specific, so that by means of this method it can be determined in a few hours whether a reaction is positive or negative.

G. BLECHMANN⁴⁵ found that the Pirquet tuberculin test in children aged from 1 to 15 years, when positive, is accompanied by a local glandular reaction in 56 per cent. of the cases; when negative, by a local

45. Blechmann, G.: The Adeno-Cutaneous Reaction to Tuberculin, *Rev. de la Tuberc.* 1:45, 1920.

glandular reaction in 16 per cent. The glandular swelling occurs the day after the appearance of the cutaneous reaction and usually persists for two days, though sometimes it lasts longer. When the cutaneous test is repeated, the glandular reaction is not so marked.

C. PESTALOZZA⁴⁶ tested seventy-two children for the regional cutaneous reaction. He substantiates the findings of Pisanis and other writers that reactions over the tuberculous lesions are stronger than controls made elsewhere. The explanation is that over the tuberculous lesions the lymphatics are more developed. This is, however, not a regular finding and has no significance.

H. ELIASBERG and E. SCHIFF⁴⁷ made a study, based on the researches of Wildbolz, who found in the urine of patients with active tuberculosis a specific antigen, which caused a tuberculin reaction at the site of vaccination. In preparing the urine, the authors followed the technic of Wildbolz. It was obtained in a sterile manner and evaporated to one-tenth its volume in a vacuum. The temperature of the water bath could be raised to only 70 because of the danger of destroying the tuberculin-like substance. After a cooling process the urine was filtered through a filter saturated with a 2 per cent. solution of phenol. Directly after the injection there appeared a large wheal with a large surrounding area of hyperemia. This traumatic reaction disappeared in from one to two hours. The character of the reaction was decided in forty-eight hours. A positive reaction consisted of redness and infiltration, which depended on the substance resembling tuberculin in the urine. A central superficial necrosis occurred in severe reactions.

Wildbolz emphasized that a reaction is to be expected only in cases of active tuberculosis and every patient tested with urine must have a control tuberculin test.

Eliasberg and Schiff's material consisted of forty cases of various forms of tuberculosis in children. They conclude from the study that the urine reaction is specific but gives no proof as to the activity of the lesion. The results in three patients with pleuritis serosa were especially interesting. In two there was no tuberculin-like substance in the urine and in one only a very slight amount—results which make it appears questionable whether every case of pleurisy in children is of tuberculous origin.

The authors do not put so much value on the procedure as did Wildbolz, but they believe the method worth further consideration.

46. Pestalozza, C.: The Regional Cutaneous Reaction in Infants, *Pediatrics*. **28**:171 (Feb. 15) 1920.

47. Eliasberg, H. and Schiff, E.: The Wildbolz Auto-urine Reaction in Tuberculous Children, *Monatschr. f. Kinderh.* **19**:5 (Oct.) 1920.

R. OFFENBACHER⁴⁸ does not believe the Wildbolz test to be reliable, for he obtained only three positive reactions in twenty cases of active tuberculosis. In a number of instances the Mantoux test (1:10000) was positive and the Wildbolz negative, according to the writer, therefore its presence shows only a possibility of an active tuberculosis.

F. ARLOING, PIERY, LEDRU and CORDIER⁴⁹ were unable to verify Wildbolz's assertion that the uro-intradermal test allows of differentiation between active and inactive lesions. They believe the test to be of equal value with the intradermal tuberculin test.

O. IMHOF⁵⁰ reports his results with the autourine and autoserum tests for the activity of tuberculosis in eighty cases. The results of both tests, with few exceptions, coincided; but the reaction was somewhat weaker with the autourine test. Both reactions were positive in the presence of an active tuberculosis, provided the skin was sensitive to tuberculin. Both reactions were negative in nontuberculous patients. The autoserum reaction is of more value when a disturbed kidney function interferes with the excretion of antibodies.

BECKER⁵¹ uses the roentgen ray to follow the course of tuberculosis. He says repeated roentgenograms often give a surprising and characteristic picture. They sometimes show that diffuse pulmonary shadows are due not to the tuberculous process but to an inflammatory exudate in the neighborhood of one or more tuberculous areas. This is evident from the disappearance of these shadows after a number of years. Becker is of the opinion that roentgen-ray examination shows changes in the lung when clinical manifestations are entirely lacking; and that it proves also that active tuberculosis in children, if they receive proper care, can recede and leave only scar tissue.

From the study in 190 roentgenograms R. SPERLING⁵² draws the following conclusions as to the localization of the tuberculous lesions in children. The primary lesion is usually in the upper lobe and lymphatic involvement of the primary stage manifests itself by changes in the hilus glands. Apical lesions are rare. In the second stage acute generalization is frequent. In older children there is a tendency to chronic indurated forms, which more often affect the right lung.

48. Offenbacher, R.: A Study of the Wildbolz Method of Determining an Active Tuberculous Lesion, *Ztschr. f. Tuberk.* **32**:355 (Sept.) 1920.

49. Arloing, F., Piery, Ledru and Cordier: The Wildbolz Autourine Reaction, *Abstr. Rev. de la Tuberc.* **1**:183, 1920.

50. Imhof, O.: The Wildbolz Autourine Reaction as a Proof of Active Tuberculosis, *Schweiz. med. Wchnschr.* **50**:1033 (Nov. 11) 1920.

51. Becker: The Course of Tuberculosis in Childhood as Seen in Roentgen-Ray Plates, *Beitr. z. Klin. d. Tuberk.* **45**:391 (Nov. 25) 1920.

52. Sperling, R.: The Localization of the Lesion in Pulmonary Tuberculosis by Means of the Roentgen Ray, *Abstr. Zentralbl. f. d. ges. Kinderh.* **10**:64 (Dec. 14) 1920.

Isolated lesions in the left side and in both lungs increase with the age of the child. In older children the upper portions of the lungs, especially the infraclavicular regions, are often affected. The process spreads to the apex in one half of the cases. Also in older children bilateral lesions frequently occur at the base of the lung.

In the third stage cavities occur. These are usually single and unilateral and formed in the upper lobe.

D. GRINGOLD⁵³ describes a symptom which in the last seven years has been of considerable service to him in making a diagnosis of tuberculous basilar meningitis and which he calls a "reflex" strabismus. It is elicited by flexing the head on the chest, when there develops either a bilateral or a unilateral internal strabismus which lasts as long as the head is kept in a flexed position and disappears as soon as the head is relaxed. In some cases the strabismus is accompanied by a retraction of the upper eyelids and by a contraction of the pupils. The author believes a reasonable explanation of this early "reflex" strabismus is that when the head is flexed the already increased pressure at the base is suddenly augmented and causes pressure on the abducens nerve with a paresis of the external rectus, or on the oculomotor nerve, with a spasm of the internal rectus.

In twenty-three cases of tuberculous meningitis, G. GENOESE⁵⁴ examined the spinal fluid and urine for acetone. In twenty cases there was an increased amount of acetone in the urine and acetone was found in the spinal fluid. In three cases in which there was but little acetone in the urine none was found in the spinal fluid.

PROGNOSIS

J. W. LANGENDÖRFER⁵⁵ followed the fate of 269 children in fifty families of whom one parent or both were treated for tuberculosis at the Bonn Clinic. He found that 146, or 54.2 per cent., suffered from the disease of the parents. Of 119 children in nineteen families of which the father had tuberculosis, the mortality from tuberculosis was twenty-one, or 17.6 per cent. Of 150 children in thirty-one families of which the mother had tuberculosis, the mortality from tuberculosis was thirty-nine, or 26 per cent. So, when the mother was affected, the mortality was higher than when the father was affected. Langendörfer found also that the morbidity and mortality from tuberculosis were greater in large than in small families and the youngest children in

53. Gringold, D.: An Early Diagnostic Sign of Basilar Meningitis, *Arch. Pediat.* **37**:19 (Jan.) 1920.

54. Genoese, G.: Acetone in the Spinal Fluid in Tuberculous Meningitis, *Pediatrics*. **28**:449 (May 15) 1920.

55. Langendörfer, J. W.: The Fate During the War of Children of Tuberculous Parents, *Ztschr. f. Tuberk. u. Heilstättenw.* **33**:150 (June) 1920.

the family were the ones most frequently infected. The morbidity and mortality were greatest during the first five years of life and just before or after puberty.

M. M. RIBADEAU-DUMAS and H. BÈCLERÈ⁵⁶ report a case which shows that tuberculosis in infants does not always end fatally. The patient was a 13 month old baby who at 9 months had been cared for by a servant with open tuberculosis. The child developed slight temperature elevation and failed to gain in weight. There were absolute dulness and feeble respiration over the entire right lung. In the course of a month this became limited to the right scapulovertebral space, in which there also was bronchial breathing. Emaciation and whooping cough-like attacks and diarrhea developed. The Pirquet test was positive. Six years later the child again came under observation. He was well and strong and had no abnormal findings in the chest.

EICHELBERG⁵⁷ also reports two cases which show that the prognosis of pulmonary tuberculosis in young children is not so unfavorable as is usually supposed.

The first patient was taken to him when 13 months old and at that time was extremely ill. He was coughing day and night and was dyspneic and very hoarse. There was a tuberculous lesion on the right parietal bone. The cutaneous tuberculin test was positive and, in spite of practically negative physical findings, the roentgen ray showed a somewhat dense shadow over the entire right side. Under treatment the child gradually improved and a second roentgenogram, taken six months later, showed the shadow was less dense. At the time of writing the child was 21 months old and in very good condition. The voice was still hoarse and there was slightly impaired resonance over the right side. The lesion of the parietal bone was healing.

The second patient was seen at 2 years and 9 months of age. When 2 years old she was taken ill with cough, fever, loss of appetite and sweating. At first there were no definite pulmonary findings. Later the percussion note on the right side showed impaired resonance. The fluoroscope showed a definite shadow at the right apex and one extending downward from the upper part of the hilus into the right upper lobe. The Pirquet test was positive. The child was treated with heliotherapy and four months later appeared perfectly well. The roentgen-ray findings were unchanged.

56. Ribadeau-Dumas, M. M. and Bèclerè, H.: The Evolution of the Initial Lesion of Pulmonary Tuberculosis in an Infant, *Abstr. Arch. de méd. d. enf.* **23**:728 (Dec.) 1920.

57. Eichelberg: Prognosis of Tuberculosis in Childhood, *Monatschr. f. Kinderh.* **18**:123 (May) 1920.

The belief that tuberculosis in infants is always fatal has undergone a change. External tuberculous lesions in young children have been known to heal and at necropsies reparative processes have been observed in tuberculous lesions of the lungs in even very young infants. Furthermore, many times recovery from pulmonary tuberculosis in infants has been reported in the literature.

L. BENARD and R. DEBRÉ⁵⁸ have made a study of the infants of tuberculous mothers sent to the Laennec Tuberculosis Hospital with regard to the frequency of infection and the mortality of infected infants. Of fifty-eight infants, forty were found to be tuberculous. In the case of the eighteen who were free from tuberculosis, separation from the mothers took place after from eight hours to six months of contact. Of sixty-five infants of nontuberculous mothers sent to the hospital by mistake, only eight became infected, three in the hospital, two in another hospital, and three through the father.

Of the forty infants infected only twelve died. The length of contact with the mother in these cases was from two to three months; in one case thirteen days. In all of these cases death occurred in the month that followed separation.

The authors draw the following conclusions: After four months of contact with a tuberculous mother an infant is presumably infected. All infants infected by contact with their mothers do not die; if the infant is still alive one month after separation he will probably survive. This is contrary to the opinion that tuberculosis of the first year of life is incurable.

STATISTICS AND PROPHYLAXIS

J. BARTSCHMID⁵⁹ made an analysis of the histories of patients admitted to the University Children's Hospital of Munich from 1912 to 1919, in order to ascertain the effect of war conditions on the frequency of tuberculosis among the children of that city.

Six hundred and seventy-five patients were admitted in the prewar years 1912 to 1914, and 1,004 during the years 1915 to 1919. Thirty-six per cent. of the children admitted during the prewar years and 47.6 per cent. of those admitted during the years of the war gave positive tuberculin reactions. The increase did not affect infants or children between 7 and 8 years, but all others, and especially children between 3 and 4 years. The children of Munich, then, were infected earlier in war times than in prewar times. The statistics showed also

58. Benard, L. and Debré, R.: The Mode of Infection and of Prevention of Tuberculosis in Young Infants, *Bull. de l'Acad. de méd. Par.* **84**:86 (Oct. 5) 1920.

59. Bartschmid, J.: The Result of War Conditions on the Frequency of Tuberculosis in the Children of Munich, *München. med. Wchnschr.* **67**:957 (Aug. 13) 1920.

that the mortality from tuberculosis in children was increased only in 1916 and chiefly affected children from 1 to 5 years of age. This was due probably to the fact that during the first two years all able bodied men were in military service, the women at work, and the children left in care of sick and incompetent individuals.

A comparison of these statistics with those of other cities shows that during the war years there was less tuberculosis in the children of Munich than among the children of other German cities, but there was an earlier infection and an increase in the severe forms.

H. DAVIDSOHN⁶⁰ performed the Pirquet test on a large number of orphan children in an ambulatory clinic of Berlin to obtain an idea of the increase in frequency of tuberculosis during the war. During 1919, from 5.4 to 6.1 per cent. were found tuberculous, a marked increase over the figures of 1913. Moreover, infection took place at an earlier age; while in 1913, 30 per cent. gave a positive tuberculin test at 4½ years; in 1919, 30 per cent. of the children gave a positive reaction at 2½ years. There seemed to be a decrease in the number of positive reactions in the children of 5 and 6, but this was due simply to the absence of antibodies because of emaciation from improper food and not to the absence of tuberculous infection. Davidsohn found also that, when the intracutaneous test was used, a much greater number of positive reactions were obtained. His tests, then, showed, that among the 2 year old orphans every second child was infected and among the 6 year old children two of every three were infected.

E. ROMINGER⁶¹ found that in 1919 fewer children gave a positive Pirquet reaction than in previous years. Routine tests in 1917 gave 41 per cent. positive reactions; in 1918, 39 per cent., and in 1919, 31 per cent. And this occurred in spite of the material increase in tuberculosis among children since the war. Rominger believes an explanation is found in the fact that from general malnutrition there are changes in the skin which inhibit the reaction and he concludes that a negative Pirquet test is of little value and must always be followed by an intracutaneous test.

P. KESSLER⁶² has compared statistics of the number of positive Pirquet reactions in children compiled before the war with those which he has collected in the Rostock clinic since the war. He finds that among children from 1 to 2 years of age there were from three to four times as many positive reactions; among children from 2 to 7

60. Davidsohn, H.: The Increase of Tuberculosis in the Children of Berlin, *Ztschr. f. Kinderh.* **26**:178 (Aug.) 1920.

61. Rominger, E.: Experience with Tuberculin in the Diagnosis of Tuberculosis in Childhood, *Monatschr. f. Kinderh.* **18**:424 (Aug.) 1920.

62. Kessler, P.: Increase in Frequency of v. Pirquet Reactions During the War, *Beitr. z. Klin. d. Tuberk.* **44**:1 (April) 1920.

years there were twice as many, and between 7 and 10 years, one-third again as many as among children of the same age before the war.

F. GARLAND COLLINS⁶³ defines the pretuberculous child as follows: A child whose vitality remains materially lowered and in whom some or all of the following conditions persist: frequent rise of temperature, enlarged lymphatic glands, loss of weight or failure to gain in weight, chronic bronchial catarrh, loss of appetite, carious teeth with stomatitis, or a general strumous condition. Especially is this true if these symptoms are associated with a family history of tuberculosis or contact with a tuberculous person. Not all these children develop tuberculosis. A certain percentage have a high degree of resistance and respond readily to ordinary treatment, but the majority become definitely tuberculous.

Chief among the various forms of treatment are (a) open air schools, residential or daily; (b) convalescent homes; (c) boarding out in the country; (d) tuberculosis dispensaries. Of most value are the residential open air schools.

W. R. P. EMERSON⁶⁴ was able to bring 189 tuberculous children up to an average of nearly double the expected weight in a nutrition class, conducted in connection with the outpatient department of the Boston Consumptive Hospital. Emerson believes that the problem of tuberculosis is for the most part a problem of nutrition. He says that if children are made well in a sanatorium, they get health; but, if they can be made well in their own homes, they get health, health education, and character. Nutrition work, which covers a new and hitherto neglected field in medicine, must be carried on with proper authority. It cannot fit in as an adjunct to other programs; but other programs must be adjusted to fit the problem of nutrition, which is the fundamental problem of tuberculosis. With the proper cooperation of the four factors that safeguard the child's health, namely the home, medical care, the child's own interest, and the school, all children can safely be brought to normal health.

A. LEVINSON⁶⁵ discusses the questions what to do with children whose parents are tuberculous but who themselves have not contracted the disease and what to do with children who have already contracted the disease.

In regard to the first, children must not come in contact with open cases of tuberculosis. The tuberculous member of the family or the

63. Collins, F. Garland: The Pretuberculous Child, *Tubercle* 1:454 (July) 1920.

64. Emerson, W. R. P.: Nutrition Classes and Tuberculosis, *Boston M. & S. J.* 183:361 (Sept. 16) 1920.

65. Levinson, A.: Sociological Phrases of Tuberculosis in Children, *Mod. Med.* 2:539 (Aug.) 1920.

child must be removed. When the parent, or other member of the family, is a closed case, the fate of the child depends on whether the father or the mother is the offending party. If the father is tuberculous, he should be removed to a sanitarium, for no one can predict when he will become an open case; and the child should remain with the mother. If the mother is a closed case, the child should preferably be removed from the house. When possible, these children should be sent to a special home, where they can be under the supervision of a physician and nurses and where they can receive special attention.

In regard to the treatment of infected children, Levinson discusses only that of latent tuberculosis; and this depends entirely on home conditions. If home conditions are good, i. e., if the child can get plenty of sunshine, good nourishing food and enough sleeping space, and if there is no open case in the family, the child can be treated at home. A child with latent tuberculosis may be sent to school; if possible, to an open air school. Rest is one of the principle requirements of a tuberculous child.

If home conditions are not good, the child should be sent to a sanitarium. The author thinks that the founding of special sanitariums should arouse a great deal of interest among physicians and social workers.

M. KLOTZ⁶⁶ regards pulmonary tuberculosis of infants as being infectious, even when no tubercle bacilli are found in the sputum, and emphasizes that these children should not be allowed to remain in a ward with others. He reports the case of a child in a hospital ward who had coughed for two months, gave a positive Pirquet reaction, and had finally died of tuberculous meningitis. In the course of the following few months three caretakers and five children of the ward developed tuberculosis.

W. J. DOBBIE⁶⁷ agrees with all writers as to the great danger to the infant of contact infection. In children over three years of age, he emphasizes the importance of avoiding massive but not a casual infection. As immunity is essential for the welfare of the child, Dobbie believes the period between infancy and adolescence the most opportune time to invite infection for the purpose of immunization.

A. and T. STRÜBEL⁶⁸ have made an exhaustive review of the literature on the passage of immune bodies from the milk and of intestinal absorption of immune bodies; and they report their own

66. Klotz, M.: *The Danger of Infection from Tuberculosis in Infants*, München. med. Wchnsch. **67**:964 (Aug. 13) 1920.

67. Dobbie, W. J.: *The Prevention of Tuberculosis*, Am. Rev. Tuberc. **4**:23 (March) 1920.

68. Strübell, A., and Strübell, T.: *Immune Milk and Prophylaxis of Tuberculosis*, Beitr. z. Klin. d. Tuberk. **45**:38 (Nov. 25) 1920.

observations on the passage of antibodies and antigens from placental circulation and from the milk into the fetus.

They believe it certain that in women antibodies, antigens, and partial antigens pass into the fetus through the fetal circulation; and in all probability in cows. Moreover, it has been proven that antibodies and antigens, in large amounts, both in women and cows, pass into the milk. The mammary glands play not merely a passive rôle in allowing this passage of the antibodies but produce and elaborate them. Absorption of these antigens from the milk into the blood serum of calves during the first months after birth has been proved. That this is not only a passive immutivity but an active immunity of long duration is evident through the presence of a positive intracutaneous reaction. The inability to produce a positive intracutaneous test in the infant seems to be due rather to the method of experimenting than to the inability of the child to react to the tuberculin. It remains to be shown just how long this immunity lasts and from how severe an infection it protects. When this is ascertained, the authors think, a way will be found to use the milk of immune women and cows for infants and calves and a great step forward will be made in the prophylaxis of tuberculosis.

TREATMENT

M. SOLIS-COHEN⁶⁹ discusses a method to determine the appropriate dose of tuberculin for the individual child. He first makes the following test for tuberculin hypersensitiveness. Simultaneously, he injects intracutaneously, in the forearm one ten millionth mg., one millionth mg. and one hundred-thousandth mg. If no reaction occurs in from twenty-four to forty-eight hours, one ten-thousandth, one thousandth and one hundredth of a mg. are injected similarly in the other arm. If still no reaction occurs, one tenth of a mg. and 1 mg. are then injected, and, if necessary, at a still later time 10 mg.

The smallest dose that produces a distinct local reaction the author administers therapeutically either by mouth or subcutaneously. If this dose causes increase of appetite, reduction of temperature, a general feeling of improvement, it is repeated every three or five days until it loses its effect, when it is gradually increased until a favorable reaction is again produced. If no general reaction is produced by the smallest dose which causes a local reaction it is repeated for several weeks and is then increased. Should any dose produce an unfavorable reaction, such as rise of temperature, anorexia, malaise, it is reduced. At intervals tests for hypersensitiveness are again made by injecting intracutaneously into the forearm the dose the patient is taking and doses one-tenth of and ten times this amount.

69. Solis-Cohen, M.: A Method for Determining the Appropriate Dose of Tuberculin for the Tuberculous Child, *Arch. Pediat.* **37**:641 (Nov.) 1920.

If no reaction occurs from any of these, one hundred times, one thousand times and ten thousand times the amount the patient is taking is injected intracutaneously. If the amount producing the intracutaneous reaction is greater than the amount which is being given therapeutically the latter dose is increased rapidly until it corresponds with the former.

The author uses tuberculin Rückstand (T.R.) for the injections. He reports the value of this method in nineteen cases in children whose initial doses varied from one hundred-millionth to one hundredth mg. and were increased from ten to 120,000 times over a period of from one to twenty-one months, practically without producing an unfavorable reaction in any case. A large proportion of the children showed improvement in general condition, reduction in temperature and gain in weight.

R. C. HOLT⁷⁰ believes that infants are infected in early postnatal life, usually from their mothers, and that this is the time to use tuberculin injections as a curative agent. He points out that the systematic use of tuberculin in infancy has two objects: first, as a test to show how many babies are infected; and second, to be the first installment of treatment in those already infected. Whenever a child gives a positive reaction, further graduated injections should follow, until a reaction fails; and the weight should be used as an index of the effects of the tuberculin. In this way, then, one could secure reasonable assurance that every child a year old is free from tuberculosis. Probably a second test would be necessary for those still exposed to infection. Holt suggests injecting one-fifth of one millionth of 1 c.c. for an infant aged 3 months. Most tuberculous babies show a rise in temperature of 2 degrees during the first six hours after the injection.

J. GRACIA DEL DIESTO and B. CORDEO⁷¹ advocate the intradermal tuberculin treatment of tuberculosis in children. They have used it for three years and find it free from dangers and difficulties of the subcutaneous method. Their technic is as follows: A needle from 1½ to 2 cm. long, with a short, sharp end, which easily stays in the skin, is used. Six solutions are made. The first contains one part of tuberculin and nine parts of a solution of ½ per cent. sodium chlorid and ½ per cent. phenol; the second contains one part of this solution and nine parts of the phenol-sodium chlorid solution; the third contains one part of solution No. 2 and nine parts of the phenol-

70. Holt, R. C.: A Plea for the Tuberculinization of Babies, *Tubercle* 2:54 (Nov.) 1920.

71. Gracia del Diesto, J. and Cordeo, B.: Intradermal Tuberculin Treatment of Pulmonary Tuberculosis in Children, *Arch. Espan. d. Pediat.* 4:20 (Jan.-Feb.) 1920.

sodium chlorid solution, etc. Only 1/10 cm. of the solution judged best for the case is used for the first injection. In cases of tracheo-bronchial adenopathy, as the sensitiveness to tuberculin is slighter than in pulmonary forms, the more concentrated solutions can be used in the beginning of the treatment. According to Jeanneret, the diameter of the macule which results from the injection should not be more than from 10 to 15 mm. If it is, a weaker solution must be used; but the authors generally obtained a macule of from 20 to 30 mm. Injections are given once a week. If symptoms of anaphylaxis, as increased in size of papule with each injection, temperature, and loss of weight, arise the treatment is stopped. Weight is a valuable criterion of the benefit or harm of the tuberculin treatment. The authors are well satisfied with the results obtained by this method.

H. MUCH⁷² has lately published a monograph (translated by M. Rothschild) on the diagnosis and the treatment of tuberculosis in children. In it he goes into detail with regard to the so-called partial antigen treatment of Deycke-Much, and he says there can be no cure without immunity, while progress in treatment depends on the maintenance of immunity. His partial antigens, by which immunity is maintained, are obtained by so treating cultures of tubercle bacillus that the acid-fastness of the bacilli disappears and there is obtained a substance which is referred to as M. Tb. By filtering M. Tb. a water soluble substance, containing the toxin of the tubercle bacillus, is obtained. This represents the pure tuberculin and is designated as L. The water-insoluble residuum is called M. Tb. R. and by treating this with alcohol and ether the three partial antigens are obtained. The portion soluble in alcohol contains the fat acid lipoids and is called by the author F.; the portion soluble in ether contains the neutral fats and is called N., the insoluble portion belongs to the group of nucleo-proteins and is designated as A. Only the M. Tb. R. and the special antigens A. F. N. are used in the treatment of tuberculosis.

Before treatment is started, intracutaneous injections are made with the partial antigens, in order to determine to which the patient is already immune and the degree of immunity. The degree of immunity is shown by the size of the papule and surrounding inflammatory area which results from the injection. If a positive reaction is obtained with N. partigen and a negative reaction with A. partigen, the patient is treated chiefly with A. partigen. Very small doses only are used for treatment. The author believes this method to be of special value in the treatment of bronchial gland tuberculosis.

72. Much, H.: *Tuberculosis in Children; Its Diagnosis and Treatment*, Translation by M. Rothschild, MacMillan Comp., 1921.

R. PIPEL⁷³ reports his experience with the partigen treatment of tuberculosis in children. His observations were made on thirty-two children from 3 to 12 years of age. Twenty-six had pulmonary tuberculosis, four had bronchial gland tuberculosis, one had osseous tuberculosis, and one had peritoneal tuberculosis. Five of the children with pulmonary tuberculosis were dismissed as cured and fourteen with the condition improved. In three the condition remained stationary, in two it became worse. Five children died.

In the four children with bronchial gland tuberculosis the general condition improved but the roentgen-ray findings remained unchanged. The child with osseous tuberculosis improved and the one with tuberculosis peritonitis died. Pipel's therapeutic results, on the whole, were favorable, but no more so than results observed in another group of patients under observation at the same time.

A. CZERNY and H. ELIASBERG⁷⁴ have treated the cachexia of tuberculous children with a foreign proteid (horse serum) in the hope of increasing their resistance. At first 10 c.c. was injected twice a week but as severe anaphylactic manifestations were obtained from 1 to 2 c.c. daily were given instead. Thirty very sick practically moribund children, suffering from pulmonary and abdominal tuberculosis, were treated in this way. In twelve good results were obtained. The children looked better, gained in weight, and no longer had fever. These results were obtained only after weeks of treatment. The treatment with horse serum influenced also the manner in which the children reacted to the tuberculin test. Children who gave a "cachectic" reaction before treatment later gave a normal tuberculin reaction. Focal reactions were never observed in the tuberculous lesions.

H. ELIASBERG⁷⁵ recommends establishing a pneumothorax in pulmonary tuberculosis in infants and children. At first he used the procedure in children with advanced lesions only but later also in those with early lesions; at first, too, only in those with unilateral, but later in those with bilateral lesions. In instances of bilateral lesions the lung more severely affected was treated first, then the other. The author obtained favorable results in cases of hilus tuberculosis and pulmonary tuberculosis with cavity formation. Until the attempt is made, it is impossible to tell whether a pneumothorax can be produced or whether the pleural cavity is obliterated by adhesions. At first nitrogen was used, later atmospheric air. To be of any value, the

73. Pipel, R.: Review of Experience since 1917 with Partigen Treatment of Tuberculosis in Children, *Wien. klin. Wchnschr.* **33**:402 (May 6) 1920.

74. Czerny, A. and Eliasberg, H.: The Treatment of Tuberculous Cachexia with Foreign Proteid, *Monatschr. f. Kinderh.* **19**:107 (Oct.) 1920.

75. Eliasberg, H.: The Treatment of Tuberculosis in Children with Pneumothorax, *Monatschr. f. Kinderh.* **19**:105 (Oct.) 1920.

pneumothorax must be maintained, until the lungs are healed—for a period, that is, of at least two or three years.

W. BAENSCH⁷⁶ has used tebelon with nineteen patients, mostly children, suffering from bone, joint, gland and skin tuberculosis. Tebelon is a preparation consisting of the isobutyl esters of fatty acids of tubercle bacillus. Stoeltzner, who first isolated the substance, believed it stimulated the production of antibodies. Baensch injected 1 c.c. into the back every third day. No ill effects attended its use. From his experience the author thinks that tebelon is not a specific for tuberculosis but that it shortens the duration of surgical tuberculosis in children.

A. REUTER⁷⁷ reports his results with tebelon, which extended over a period of seven months. He used 1.1 c.c. twice a week. The greatest number of injections was thirty-eight. From this experience Reuter believes tebelon is an indifferent agent and has no effect on the human organism.

The experience of F. LEHNERDT and M. WEINBERG⁷⁸ with tebelon extended over a period of three years. In all there were treated ninety patients of whom ten were adults with acute phthisis; eight had lupus; thirty-three were children with severe clinical tuberculosis; thirty-seven were children with scrofula. The conclusions drawn from the study were that tebelon has no influence on tuberculosis in adults; it has a favorable effect on lupus but this is not permanent. It has no effect on pulmonary tuberculosis of childhood, when at an advanced stage. Its use is only advised when the process is well localized and the children are in good physical condition. In scrofula, however, it seems to be a very useful remedy, a favorable influence was observed in all the cases. At first there was a softening of the infiltrations of the skin or glands—then the secretion gradually stopped—all inflammatory areas showed a tendency to granulate and healing took place more quickly than was expected. Scrofulous eczemas and phlyctenular conjunctivitis were soon cured. Swelling of the glands disappeared and the general condition of the patient improved.

A. DU FOURT⁷⁹ advises heliotherapy in the treatment of mediastinal adenopathy in children. The treatment is begun by exposure of the lower extremities. After the eighth day the chest is exposed for five minutes daily and, if the treatment is tolerated, the exposure is increased

76. Baensch, W.: Tebelon in the Treatment of Surgical Tuberculosis, München. med. Wchnschr. **67**:1009 (Aug. 27) 1920.

77. Reuter, A.: Treatment of Tuberculosis in Children with Tebelon, Monatschr. f. Kinderh. **19**:34 (Oct.) 1920.

78. Lehnerdt, F. and Weinberg, M.: Tebelon in the Treatment of Human Tuberculosis, Ztschr. f. Kinderh. **26**:215 (Sept. 13) 1920.

79. Du Fourt, A.: The Treatment of Mediastinal Adenopathy with Heliotherapy, Arch. de méd. d. enf. **23**:436 (July) 1920.

to two hours daily. Pulse and temperature must be watched closely. If there is pulmonary as well as gland involvement, the child should be put to bed for a week before the treatments are begun; and thoracic exposure should never exceed ten minutes.

In mediastinal gland tuberculosis physical signs and roentgen-ray shadows usually disappear in four or five months, but, if there is pulmonary disease, the duration is much longer. In some patients heliotherapy seems to aggravate the glandular condition and is contra-indicated. Young infants do not stand the treatment well. Erythema and a rise of temperature to 39 or 40 C. are warnings against too long exposures.

I. S. TROSTLER⁸⁰ recommends the roentgen-ray treatment in tuberculous adenitis. When no breaking down or liquefaction has taken place, brilliant results are the rule in 80 per cent. of the cases. Even when the glands have broken down and are draining, the roentgen ray will often produce reduction in size and softening of the scar tissue. If the glands have broken down and are not draining, it is better to aspirate the contents, before treatment is commenced. Aspiration can be repeated as often as fluid appears. A very useful and efficient adjunct to roentgen-ray treatment in cases in which suppuration has continued for a long time is the swabbing out of the sinus with a mixture of equal parts of phenol and tincture of iodine.

C. E. FIELD⁸¹ does not advocate radium to take the place of surgery in the treatment of tuberculous adenitis but believes it to be of great value in the treatment of this condition. In thirty-two patients treated during four years the process was arrested and apparently cured in twenty-seven; three patients were lost sight of, and one died from pulmonary tuberculosis two years after treatment.

H. GAUVAIN⁸² describes the Teloar Crippled Hospital for tuberculous children. The place was chosen because of abundant sunshine, extensive shore line with considerable tidal excursion, sandy soil, slight or moderate rainfall, lack of trees, clear atmosphere free from dust, hills protecting from the cold and winds, bracing climate, beach adequate for unrestricted use of the patients. The hospital itself has an extensive veranda so constructed that the patients need not leave it, even during rain, and especially designed awnings pull down over the beds; the mattresses are heated by electricity, which is the best and most labor-saving method of keeping the patient comfortably warm.

80. Trostler, I. S.: The Treatment of Tuberculous Adenitis with Roentgen Ray, *Am. J. Clin. Med.* **27**:804 (Dec.) 1920.

81. Field, C. E.: The Treatment of Tuberculous Adenitis with Radium, *Long Island M. J.* **14**:424, 1920.

82. Gauvain, H.: The Care of Tuberculous Children, *Brit. J. Tuberc.* **14**:49 (April) 1920.

A valuable feature of the institution is the postgraduate course in surgical tuberculosis.

T. H. MARTIN⁸³ describes the hospital school for the treatment of surgical tuberculosis in children at Seasowe-Cheshire. It is built within 300 yards of the sea, fully exposed to winds which sweep from the Irish Sea. It is constructed on the block parallel system. Each block consists of two stories with twenty-four to thirty beds on each floor. The wards face due north and are light and airy. On the southern aspect are large sun balconies on which beds are always kept, except in the severest weather. Abundance of fresh air, sunshine and good food are the principal factors in treatment. Great importance is placed on heliotherapy. Carefully planned school-work with hospital treatment has proved a great success.

A. W. HOLLIS and I. H. PARDEE⁸⁴ have collected from the literature reports of thirty-eight cases of tuberculous meningitis with recovery of the patient and report two cases of their own. They report two other cases in which a probable diagnosis of tuberculous meningitis was made. Their method of treatment was to use intraspinal injections of antimeningococcic serum with frequent spinal drainage. They consider that intraspinal injections of antimeningococcic serum have two distinct actions. First it adds to the spinal fluid certain antibodies, which it is unable to develop itself and second it introduces within the dura a foreign proteid in the form of horse serum.

83. Martin, T. H.: The Hospital School for Treatment of Surgical Tuberculosis in Children, *Brit. J. Tuberc.* **14**:145 (Oct.) 1920.

84. Hollis, A. W. and Pardee, I. H.: Recovery from Tuberculous Meningitis after Treatment with Intraspinal Injections of Antimeningococcic Serum, *Arch. Int. Med.* **26**:49 (July) 1920.

CHRONIC DIFFUSE NEPHRITIS IN CHILDHOOD

REPORT OF A CASE WITH A REVIEW OF THE LITERATURE*

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Chronic diffuse nephritis during childhood is a rare condition though of no less interest because of its infrequent character. The possibility of its occurrence was first suggested in 1872 when Gull and Sutton¹ described a case of "contracted kidneys" in a 9 year old girl. Its actual occurrence was confirmed two years later by Barlow² who gave the first complete case report of this condition. Since the time of Barlow, a gradually increasing number of cases have been reported, particularly in England where the name of "renal infantilism" has tended to emphasize the associated general bodily changes, as well as the original kidney lesion. In Germany, likewise, there has been a series of similar case reports. Under these conditions it would seem desirable that the whole field be surveyed, all available cases reviewed, and the findings correlated. This has been attempted in the present paper. The clinical and pathologic findings in an additional case are presented.

REPORT OF CASE

B. M., Harriet Lane Dispensary, No. 24,377; age 4 years, of American parentage. Complaint: "Nervousness, convulsions and vomiting."

Family History.—Unimportant. There was no history of nephritis in either parent. The mother had four miscarriages.

Past History.—Full term child, spontaneous labor. Feeding was difficult during the first year and the gain in weight was slow. She had frequent attacks of bronchitis but no measles, scarlet fever, or other infectious diseases.

Present Illness.—March 7, 1920, an eruption was noticed on the chest. This was called measles by the family physician. By March 14 the eruption had disappeared, but the child was drowsy and vomited solid food. She was thought to have had fever from March 7 to March 14. No change in her condition occurred until March 27, when her eyes became crossed. She was admitted to the Harriet Lane Home, March 28.

* Received for publication, Nov. 26, 1921.

* From the Harriet Lane Home, the Johns Hopkins Hospital.

1. Gull, Sir W. W. and Sutton, H. G.: On the Pathology of the Morbid State Commonly Called Chronic Bright's Disease with Contracted Kidney, *Med. Chir. Tr.* **55**:273, 1872.

2. Barlow, W. H.: Notes and Remarks on a Case of Granular Contracted Kidney (Cirrhosis of the Kidney in a Child of Five Years and Eleven Months), *Lancet* **2**:151, 1874.

Physical Examination.—A very ill child. Temperature 100.8 F.; pulse, 120; respirations, 32. Very drowsy. She had a left sided convulsion shortly after admission. No rash was present but there was a fine scaly desquamation over the back. No general glandular enlargement was present.

Head: Anterior fontanel admitted one finger tip. The frontal bosses were prominent. Eyes negative, no strabismus or nystagmus. Pharynx slightly injected and tonsils hypertrophied.

Chest: Chest showed moderate costochondral beading.

Lungs: The lungs were clear on percussion and auscultation.

Heart: Systolic heave. The point of maximum impulse was in the fifth interspace outside of the mamillary line. A systolic murmur was present at the apex and over the precordium.

Abdomen: Muscle tone was fair. The liver and spleen were not felt. The bladder was distended.

Extremities: Muscular development was poor. Following the convulsion the limbs were flaccid. Slight twitching of the right hand and arm occurred during the examination.

Reflexes: The knee jerks were absent on admission. Later both superficial and deep reflexes were present and bilateral ankle clonus was obtained.

Ophthalmoscopic Examination: There was slight haziness of the nasal portion of both discs with moderate engorgement of vessels.

Lumbar puncture: Clear fluid under an increased pressure was obtained. Tests for globulin were negative; two cells per cubic millimeter.

Laboratory Examination.—Urine: A catheterized specimen was clear, straw colored and acid; specific gravity, 1.018; albumin, positive; sugar, negative; acetone, faint trace; guaiac, negative. Microscopic examination showed frequent leukocytes but no casts.

Leukocytes: 18,200.

Wassermann, negative.

Course in Hospital.—The patient was admitted with a temperature of 100.8 F. Shortly after admission she had a convulsion lasting three minutes and involving the left side of the body. During the convulsion there was twitching of the left eyelid and face, and clonic spasm of the left arm and leg. Chloroform was used to control the convulsion, followed by morphin. Later the child developed hyperpnea and the breath had a sweetish odor. The bicarbonate capacity of the blood serum was 14 volumes per cent. Sodium bicarbonate was given by gavage in 60 grain doses at 8:30 p.m., 11 p. m., and 12 m., and 5 per cent. glucose was administered by Murphy drip. The child remained comatose March 29 with a temperature at noon of 98.8 F. and at 3 p. m. of 105.4 F. Died at 4 p. m.

Report of Necropsy.—Necropsy No. 6,195.^a Body was that of a well developed, well nourished, female white child. The serous surfaces of the abdominal cavity were smooth and glistening, there was no excess of fluid. The thoracic organs were normally situated. The pleural cavities showed a smooth and glistening surface and contained no excess of fluid. There was a moderate sized thymus weighing 5 gm.

Heart: The pericardial lining was smooth and glistening. The pericardial fluid was of a clear straw color and not excessive in amount. The heart appeared to be somewhat enlarged. The epicardium was smooth and glistening. The myocardium was of normal consistency and the usual color. The cut surface showed nothing unusual. The wall of the left ventricle was somewhat hypertrophied. The cardiac chambers however were not dilated. The endocardium was smooth and glistening. The valves were normally formed. Those on

3. Necropsy by Dr. J. R. Cash of the Department of Pathology. I am indebted to Dr. Cash for permission to report the pathologic findings in this case.

the right side of the heart were delicate and translucent. The mitral valve was also quite delicate but contained two small patches of atherosclerosis in its center. The edges were slightly thickened but apparently this did not interfere with the function of the valve. The aortic valves were appreciably thickened. Their size had not been reduced, however, and there was apparently no change in their function. In the sinuses of Valsalva there was a definite atherosclerosis which extended a short distance up the ascending arch of the aorta. The coronary arteries were unobstructed and their intima was undamaged. Weight, 100 gm.

Lungs: The right lung weighed 105 gm.; the left, 140 gm. Both lungs were of similar appearance. The pleural surface was smooth and glistening. The upper lobes were quite crepitant throughout. The lower lobes were somewhat less so and contained numerous red elevated circumscribed areas of consolidation. The bronchi showed slightly injected walls and contained a slight amount of mucus.

Spleen: Weighed 20 gm. and measured 9x3x2 cm. It was normal in shape, size and position. The capsule was smooth and glistening and not thickened. On section the cut surface was of a dark mahogany color, quite firm, and did not readily scrape away with the knife. The malpighian bodies were very distinct. The interstitial connective tissue was not increased in amount.

Pancreas: Weighed 25 gm., length 12 cm. It was normal in shape, size, position and consistency.

Liver: Weighed 560 gm. and measured 19x13x4 cm. It was normal in shape, size and position. There were no external signs of scarring or other degenerative changes. On section the liver cut normally. There was no scarring, hemorrhage, necrosis, or fatty change to be made out.

Suprarenals: Weight, together, 7 gm. They were normal in shape, size, position and consistency. On section no unusual changes were seen.

Kidneys: The right kidney weighed 17 gm., the left kidney, 19 gm. The kidneys were quite small and extremely pale. Their surface was marked by many large and small scars giving a rough granular appearance. There were numerous small cysts over the kidney surface. The capsule was stripped with great difficulty leaving a rough torn surface but with no hemorrhages to be seen over it.

On section both kidneys had a similar appearance. The cut surface was extremely pale and of a yellowish-white color. The kidney architecture was not distinct. The cortex was very much thinned, in some places measuring only 2 mm. in thickness. The glomeruli could not be seen. The cortical striations could only be seen in a few areas and here they were quite indistinct and irregular. The pyramids were fairly well developed but the tubules were irregularly arranged. There were no areas of hemorrhage to be seen in either kidney. The pelves were of normal size and their interior surfaces were smooth and glistening. The ureters were normal in all respects.

Pelvic organs: The bladder walls were of normal thickness. The mucous membrane was smooth and glistening, delicate, and everywhere intact.

Brain: The meninges were delicate but presented no adhesions. Externally the brain showed nothing unusual. No exudate was seen at any point on the brain surface.

MICROSCOPIC NOTES

Kidneys: The surface was irregular and numerous old scars could be seen beneath it. The glomeruli showed marked changes. There were many adhesions between the capillaries and Bowman's capsule. Many glomeruli were obliterated or partly obliterated by scar tissue and showed hyalin degeneration. Throughout the kidney substance and especially in the cortex there was a dense infiltration of round cells. Many of these appeared to be lymphocytes but many wandering cells could be seen among them. The tubules were distorted by diffuse scarring and many of them contained blood and polymorphonuclear

leukocytes. Many tubules were compressed or obliterated by the scarring and cellular infiltration. Most of the others were dilated. The pelvis appeared normal though just beneath the pelvic epithelium a slight infiltration of wandering cells was noticed.

Lungs: The alveoli were filled with coagulated fluid. A few red blood cells polymorphonuclear leukocytes and epithelial cells could be seen within the alveoli and small bronchi. The lymph follicles surrounding the bronchi showed some hyalin change in their central portions.

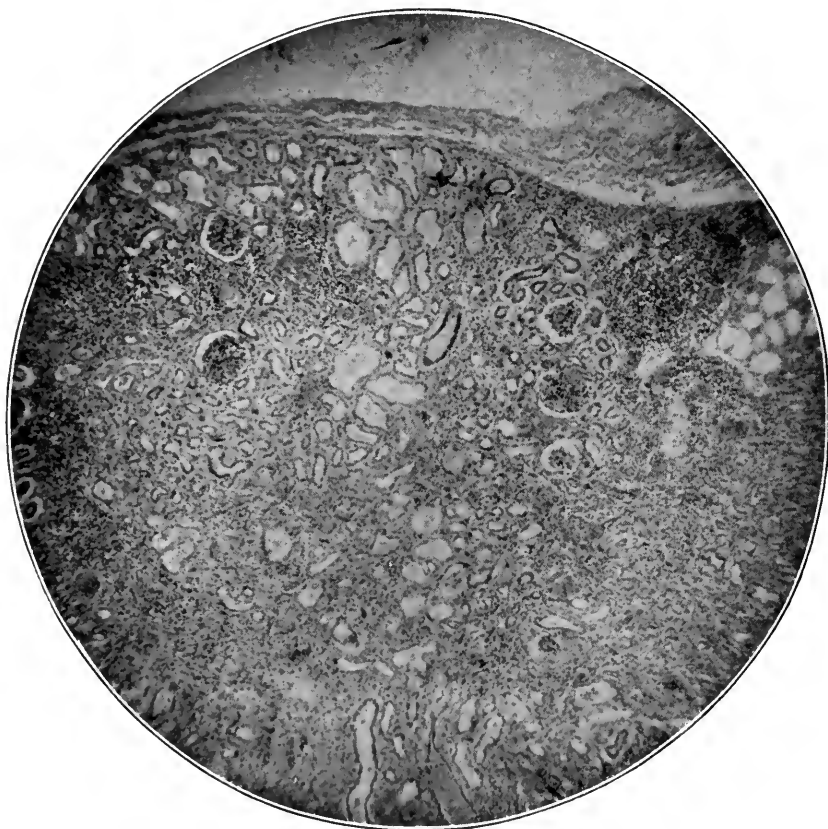


Fig. 1.—Cortex of the kidney showing the well marked interstitial nephritis. The atrophy of the glomeruli, the dilatation of the tubules and the round cell infiltration with scarring are characteristic.

Spleen: The malpighian bodies were very distinct and somewhat enlarged. The sinuses were engorged with blood.

The heart, pancreas, thymus, suprarenals, lymph glands and liver were normal.

Previous reports of chronic nephritis in childhood have varied greatly in value. Many have been simply case histories, without pathologic study of the kidneys. In any case of primary nephritis in childhood the clinical history is of great importance in judging the

nature of the renal lesion. The earlier collections by Sawyer⁴ or Nettleship,⁵ of cases of chronic nephritis in children, were made with but little discrimination. They included practically all cases to be found in the literature at the time. In many of these cases the history clearly indicated the presence of a definite secondary nephritis. In other cases the history was so defective that the possibility of a secondary nephritis could not be excluded.



Fig. 2.—Glomerulus showing the atrophic condition of the tuft. The partially dilated tubules and the round cell infiltration are also shown.

All cases with a history of scarlatina must be excluded rigidly in any critical study of primary nephritis in childhood, though there is no similarity between the clinical picture of a chronic diffuse

4. Sawyer, J. E.: *The Etiology of the Granular Kidney of Childhood*, St. Thomas Hosp. Rep. **35**:459, 1906.

5. Nettleship, E.: *On Renal Retinitis in Young Subjects and on the Relative Frequency of Juvenile Interstitial Nephritis in the Two Sexes*, Roy. Lond. Ophth. Hosp. Rep. **16**:1, 1904.

nephritis and a postscarlatinal nephritis. Syphilis likewise must be excluded as chronic renal change is occasionally found in the congenital syphilitic.

In the present report these criticisms have been kept in mind and an effort has been made to present only those cases in which the histories show a more or less uniform clinical picture. In most instances the symptomatology can be traced from the first year of life if not, actually from birth. An effort has also been made to rule out preceding infections that might play a rôle in the development of the nephritis. With the exceptions noted in the abstracts, all cases with histories of scarlatina or syphilis have been carefully excluded. In addition a complete pathologic report with a description of the renal changes has been felt desirable, owing to the confused state of the nomenclature in renal pathology. Furthermore, with increasing age the history becomes of progressively less value in excluding conditions which may be the determinants of the later nephritis. This study, therefore, was arbitrarily limited to children under 10 years of age.

A search of the literature has revealed the reports of nineteen cases meeting the requirements mentioned. Reference should also be made to eight other cases of apparently the same condition, but in which the reports lack completeness.

REVIEW OF LITERATURE

1. Cases of chronic diffuse nephritis with reports of the complete clinical and pathologic findings.

WEIGERT, 1879.⁶—A 6 weeks old infant. The clinical pathological findings in this case included cyanosis, congenital fusion of the pulmonary valve leaflets, hypertrophy of the right ventricle and an open ventricular septum.

Further evidences of congenital disturbance were found in the kidneys which measured $1.7 \times 1.0 \times 0.5$ cm. and $2.0 \times 1.1 \times 0.4$ cm., respectively. The kidney substance was pale with the cortex greatly decreased on both sides and with many small cysts on the surface of one kidney. Microscopically the kidneys showed numerous shrunken patches with increased interstitial tissue adjoining well preserved kidney substance. The epithelium of the malpighian corpuscles was large-celled and showed fatty changes.

DEMOCH, 1902.⁷—Boy, aged 2 months. Apparently well for the first month and then was brought to the hospital for cough and laryngospasm. Physical examination showed distinct edema, especially at the ankles, an enlarged heart and palpable spleen. The urine contained albumin together with fatty and hyalin casts. Postmortem examination showed generalized anasarca, cardiac hypertrophy with dilatation, pulmonary edema with lobular pneumonia and visceral congestion.

Kidneys of equal size, $5.0 \times 3.0 \times 2.5$ cm. The consistency was increased and the capsule stripped with difficulty leaving a rough granular surface. Two

6. Weigert, C.: Die Brightsche Nierenerkrankung vom pathologisch-anatomischen Standpunkte. Sammlung Klinischer Vorträge (Volkman). **162**: 163:1460, 1879.

7. Democh, I.: Genuine Schrumpfniere im Säuglingsalter. Arch. f. Kinderh. **33**:283, 1902.

pinhead sized cysts were present on the surface of the left kidney. On section the cortex was from 3 to 4 mm. in thickness and yellowish brown in color. Microscopically the tunica albuginea of the left kidney was thickened and closely attached to the cortex. The glomeruli were of varying size but were not contracted and the capsule was not thickened. In the convoluted tubules the epithelium was swollen but the nuclei were distinct. The interstitial tissue in the cortex of this kidney showed no increase. The medullary rays were distinguishable to the periphery of the cortex and showed an increased nuclear content though there was no increase in connective tissue. In most of the tubules the epithelium was swollen, filling the lumen, though there were some dilated tubules filled with hyalin material. The vessels showed an indefinite slight thickening of the media and adventitia. A few small hemorrhages were present between the cortical convoluted tubules.

Compared to the left kidney the right showed an increase in interstitial tissue. Many of the glomeruli were contracted and the cortex contained many small cysts arising from degenerated or destroyed glomeruli. The convoluted tubules were dilated and their epithelium was degenerated. The medullary substance was mottled with the heaping up of fresh connective tissue rich in blood vessels and showed occasional hemorrhages. The process had more of a parenchymatous character than that in the left kidney.⁸

HELLENDALL, 1897.¹⁰—Girl, aged 6 months. This child, the younger of two similarly affected sisters, was weak and sickly from birth. She died at the age of 6 months from infantile atrophy following measles. Necropsy showed bronchopneumonia and enteritis.

The kidneys were very small but of similar size, $3.3 \times 2.0 \times 0.6$ cm., and weighed 4.0 gm. each. The surface was hyperemic and distinctly granular. The cortex was pale yellowish, the medulla cyanotic. A pea-sized cyst was present on the surface of the right kidney. The intracapsular space in the glomeruli was wide and the tufts small and shrunken. The glomeruli varied greatly in size, those lying near the surface showing marked changes with thickened capsules and degenerated loops. The nearer the glomeruli to the medulla the larger and less changed they were. There was cystic dilatation of the convoluted tubules with flattening of the epithelium. The larger arteries also showed thickening of the adventitia. In addition to the interstitial changes, Helledall describes five chondromata in the renal cortex.

FRÖLICH, 1904.¹¹—Girl, aged 15 months. The parents of this child were well but a maternal uncle died of chronic nephritis, and an older sister born two years previously was similarly affected. Symptoms were first noted at

8. In her discussion of this case Democh pointed out the difficulty in differential diagnosis between a primary and secondary nephritis. She thought the nephritis was of congenital origin though there was a possibility of its being secondary to the preceding gastro-enteritis. Borrmann⁹ in a later discussion of this case dismisses the possibility of gastro-enteritis as a cause of the nephritis and because of the unilateral character of the nephritis considers it secondary to an ascending pyelocystitis. There was no evidence at necropsy of such a condition. In view of the fact that the child was apparently well up to the onset of the gastro-enteritis at the age of one month and died 4 weeks later, the author agrees with Democh in considering the nephritis as of probable congenital origin.

9. Borrmann, R.: Harnapparat. In Handb. d. allg. Pat.h. u. path. Anat. d. Kind. (Brüning-Schwalbe) Wiesbaden. 2:227, 1913.

10. Helledall, H.: Hereditære Schrumpfnier im frühen Kindesalter. Arch. f. Kinderh. 22:61, 1897. (Case 2.)

11. Frölich, T.: To tilfælde af hereditær, familiaer, kongenital (?) nefrit. Norsk. Mag. f. Laegevidensk. 5:905, 1904; abstracted in Jahrb. f. Kinderh. 64: 244, 1906. (Case 2.)

two weeks. The infant did not gain in weight and albumin and casts were found in the urine. Later the child developed periodic attacks of vomiting. At necropsy hypertrophy of the left ventricle and pneumonia were found.

The kidneys were small, weighing right 18 gm. and left 17 gm. The surface of the right kidney showed fetal lobulation but was smooth. The left was slightly granular with shrunken contracted areas on the surface. The left kidney showed slight dilatation of the pelvis and the first portion of the ureter. Sections of the most normal kidney showed an extensive degeneration of the tubular epithelium. Some of the tubules were filled with hyalin casts. The glomeruli in the deeper layers of the cortex showed beginning contracture with slight changes in the surrounding stroma. The stroma was normal throughout the rest of the parenchyma. Single dilated tubules were present in the superficial layers of the medulla. Sections from the more contracted kidney showed a striking increase in the stroma with clumps of round cell infiltration. In these areas the glomeruli were atrophic and contracted and occasionally showed hyalin degeneration. The tubular epithelium was degenerated and single tubules were dilated and filled with a granular coagulum. There was a general thickening of the stroma with areas of round cell infiltration and connective tissue increase.

PATERSON, 1920.¹²—Boy, aged 1 year and 9 months. This boy was apparently well at 11 months, though undersized. He refused solid food. Rachitis-like deformity appeared at this time and progressed to an extreme degree. For six months previous to admission he had irregular attacks of vomiting associated with loss of weight, so that he only weighed 10½ pounds when first seen. Uremia and death followed a change to a solid diet with meat.

The left kidney was extremely small and cirrhotic. The right kidney was slightly larger but was also abnormal. Its condition suggested an old inflammation. The weight of the kidneys was 27 gm. each. Microscopically they showed a marked degree of fibrosis, the kidney substance in some areas being entirely replaced by fibrous tissue. Many of the glomeruli were obliterated and in some places the tubules showed enlargement as though in an early stage of cyst formation. The arteries were greatly thickened.

HELLENDALL, 1897.¹³—Girl, aged 2 years. An older sister of the other child reported above.¹⁰ She likewise was weak and sickly from birth. Backwardness in development was marked and at the age of two she could neither walk nor talk. Marked rachitic deformity was present. Besides the defective development it was noticed that she drank a great deal, especially at night. In addition she had occasional attacks of vomiting and of swelling of the feet. No cardiac hypertrophy was observed at necropsy following death from bronchopneumonia.

The kidneys were very small, of about the same size, 4.0 x 2.5 x 0.7 cm. and weighed 6 gm. each. The surface was granular with yellow flecks. Pinhead sized cysts were seen on the surface of the left kidney. The glomeruli were irregular in size, some normal, some enlarged with a cellular increase, and still others shrunken, poor in cells and surrounded by a fibrous ring. The convoluted tubules are in part slightly, in part markedly dilated. Fatty metamorphosis was present in the convoluted tubules. Around the glomeruli the interstitial tissue was arranged in broad fibrous bands while in other parts it was less well developed, more wavy and richer in nuclei. In the medulla there was a marked increase in connective tissue between the tubuli recti which were crowded together, but they did not show as marked a change as in the cortex. The increase in connective tissue was a diffuse and not a localized process. The blood vessels showed nothing unusual.

12. Paterson, D. H.: Three Cases of Renal Dwarfism Associated with Curious Bony Changes, *Proc. Roy. Soc. Med.* **13**: Sect. Dis. Child., 107, 1920 (Case 2).

13. Helledall, H.: *Arch. f. Kinderh.* **22**:61, 1897 (Case 1).

HEUBNER, 1913.¹⁴—A 3 year old child. Heubner reports that in all of his experience he only saw one case of "Schrumpfnieren" in the strictest sense of the word. His original report could not be obtained but in this later abstract he reports a case of idiotic child of a father suffering from lead poisoning. There was no edema. The pulse was irregular. The urine showed marked albumin and many granular casts. Section showed an enormous contraction of both kidneys with diminished amount of parenchymatous tissue and dilated tubules.

MILLER AND PARSONS, 1912.¹⁵—Girl, aged 3 years and 6 months. She was pale, cyanotic and wasted, being markedly underdeveloped and weighing but 16 pounds. Clinically, polyuria and polydipsia had been noticed as well as the occasional presence of a variable degree of edema. The urine had a specific gravity of from 1.001 to 1.004 with a trace of albumin, but no casts. At necropsy there was slight hypertrophy of the left ventricle.

The kidneys each weighed approximately 30 gm. The changes in the kidneys were described as being the same as those in the 6 year old girl described by the same authors.

OFFENHEIM, 1891.¹⁶—Boy, aged 4 years. Polyuria was the first symptom noticed and was observed early in life. Later headache and nausea were present. In the hospital the child was feverish, vomited a great deal, and complained of headache. His appetite was poor and feeding was difficult, with the result that his weight fell from 11.9 to 9.6 kilos. At the same time he developed diarrhea and great thirst. No edema was noticed. Dimness of vision was complained of shortly before death but no ophthalmoscopic examination was made. He died in uremic convulsions. Necropsy showed congestion and massive edema of the lungs. The heart was not enlarged.

The left kidney measured 7.5 x 3.0 x 2.5 cm. Weight, 43.7 gm. The right measured 7.0 x 3.5 x 2.5 cm. Weight, 48.6 gm. Fetal lobulation was present in both. The capsule was more firmly adherent than normal, the surface granular, and the cortex decreased in thickness. The microscopic picture was that of beginning contraction. Wedge shaped contracted areas were present, apparently rich in glomeruli because of atrophy of the interlying parenchyma. In part, the glomeruli were shrunken, with thickened capsules and cellular proliferation, or complete degeneration of the tuft. The tubules were compressed by the proliferation of the interstitial tissue. In places the tubules showed varying degrees of atrophy and there were many dilated tubules containing hyalin masses. The interstitial tissue was luxuriant, in some places more so than in others. The process was evidently only beginning, for nowhere was there heavy, fibrous scar tissue. The vessels showed distinct thickening, especially of the adventitia.

BARLOW, 1874.²—Girl, aged 5 years, 11 months. This child was always weak and delicate. She developed enuresis when about 4 years old and was later observed to have polyuria, passing from 3 to 4 pints of very pale urine daily. The specific gravity varied between 1.010 and 1.015 but albumin was only found shortly before death. No casts were found. The child died in uremic convulsions. Cardiac hypertrophy was present.

The kidneys measured 5.0 x 3.7 x 1.2 and 5.6 x 3.5 x 1.5 cm. and weighed 13.7 and 23.0 gm., respectively. A few small cysts were present in the right kidney. The microscopic examination was necessarily incomplete owing to

14. Heubner, O.: Ueber chronische Nephrose im Kindesalter. *Jahrb. f. Kinderh.* **77**:1, 1913; abstracted from *Festschr. f. von Leuthold (Berlin)* **1**:351, 1906.

15. Miller, R., and Parsons, L.: Renal Infantilism, *Brit. J. Child. Dis.* **9**:289, 1912 (Case 5).

16. Oppenheim, A.: Ueber Schrumpfnieren im Kindesalter. *Inaug. Dissert.*, Halle, 1891.

the rudimentary development of histological technic at the time, but sections showed a general fibrous tissue overgrowth and vascular sclerosis.

MILLER AND PARSONS, 1912.¹⁷—Girl, aged 6 years. She weighed 2 pounds at birth and was always small, backward and underdeveloped. Though six years old she was only 36 inches tall. She had suffered from polyuria, nocturia, and thirst for the greater part of her life and was admitted to the hospital in uremic convulsions. There was very slight hypertrophy of the left ventricle found at necropsy.

Both kidneys were small, weighing together 32 gm. and measuring 4.3 and 4.75 cm. in length and 3.0 cm. in breadth. The capsule was slightly thickened but stripped easily leaving coarsely granular surface. The cortex was greatly diminished, from 4 to 6 mm. in thickness. Histologically, the glomeruli varied greatly in shape and size. A few were completely sclerosed. Others showed fibrotic changes with capsular adhesions. The condition in the tubules was apparently secondary to the interstitial change. The tubules were irregularly dilated and some appeared to be cystic. The epithelium was healthy, however, except for flattening from pressure. There seemed to be no active parenchymatous changes. The interstitial tissue was much increased. The new formed connective tissue was cellular and many accumulations of small round cells were present. The vessels were moderately thickened.

PARSONS, 1911.¹⁸—Girl, aged 6 years and 6 months. Was brought in complaining of "drinking diabetes." She was a very much underdeveloped child with moderate edema of her legs and face. The urine was large in amount, pale, specific gravity 1.010 and with a trace of albumin but no casts. Death was from bronchopneumonia. Necropsy showed definite hypertrophy of the heart.

The kidneys were extremely small and together weighed less than 30 gm. Their capsules stripped readily leaving granular surfaces. The cortex was diminished. Microscopic examination showed extensive general fibrosis of cortex and medulla. The glomeruli varied in size, some being larger and others smaller than normal, and many exhibited some degree of fibrosis. Some showed hyalin changes. The epithelium of the tubules was normal in some areas, but in others was granular and desquamating. Some of the tubules also showed dilated or cystic lumina. The degree of fibrosis varied, being more dense in some areas than others, and was extremely cellular in places. The vessels showed thickening of the middle and outer coats and in some the lumina were nearly occluded. "The whole condition exhibited a degree of fibrosis as marked as, or more marked than ever obtained in the most advanced cases in adults."

JACOBS, 1913.¹⁹—Girl, aged 7 years. This patient had had scarlatina four weeks before her admission to the hospital. Nine days before admission she developed edema of the eyelids and a marked albuminuria. Death was from bronchopneumonia. Postmortem examination revealed a generalized anasarca, pulmonary edema, bronchopneumonia and cardiac hypertrophy.

The kidneys were small and firm with somewhat adherent capsule. The surface was irregular with coarse greyish granulations. They measured 5.5 x 4.4 x 2.2 and 5.1 x 3.2 x 2.2 cm. and weighed 29 and 27 gm., respectively. On section the cortex was narrow, the markings indistinct and the glomeruli visible. Microscopically, the glomeruli were enlarged, arranged in clumps, and surrounded by a cellular infiltration. There was no hyalin change. The interstitial tissue was everywhere increased. Atrophic tubules were present in the

17. Miller, R., and Parsons, L.: *Brit. J. Child. Dis.* 9:289, 1912 (Case 2).

18. Parsons, L.: *Infantilism Associated with Chronic Interstitial Nephritis*, *Brit. M. J.* 2:481, 1911.

19. Jacobs, C.: *Ueber Granularatrophie der Nieren im Kindesalter*. *Berl. klin. Wchnschr.* 50:2418, 1913 (Case 1).

subcapsular layers while in the deeper layer there were groups of normal or dilated tubules without an increase in the intervening stroma. Small focal masses of lymphocytes were strewn through the whole tissue, especially in the neighborhood of the glomeruli. The epithelium in the dilated tubules was large, swollen, and granular with desquamated cells or masses of coagulum in the lumen of the tubules. The walls of the smaller vessels were normal but the smaller arteries showed a thickened media.²⁰

MILLIGAN, 1902.²²—Boy, aged 7 years. This patient was an underdeveloped anemic child who had been weakly since birth. He suffered from polyuria and nocturia. Headaches and dimness of vision developed later. The specific gravity of the urine was 1.006 with a large amount of albumin present. Hyalin and granular casts were found in the terminal samples. His condition rapidly became worse with polyuria up to four pints a day and with increasing quantities of albumin. The headaches became more marked and ophthalmoscopic examination showed typical albuminuric retinitis. Edema developed as a sequel to cardiac dilatation and collapse. Necropsy showed moderate cardiac hypertrophy. In this case there was dilatation of the right pelvis and ureter without apparent cause.

The kidneys were granular. The right kidney was smaller than the left. A section from the left kidney showed the condition to be an advanced interstitial nephritis. The renal tubules were in places completely obliterated by fibrous tissue. Some of the tubules were devoid of their epithelial lining though the epithelium was present in others. The blood vessels showed great thickening of their walls.

GUTHRIE, 1900.²³—Girl, aged 7 years. Was weakly as an infant but except for diarrhea and measles had never been sick previous to coming under Guthrie's observation. Two months previous to entering the hospital she began to complain of frontal headaches and to suffer from attacks of vomiting. She was a thin, undersized girl. No edema was present. The heart was enlarged and the brachial arteries were palpable. The urine had a specific gravity of 1.010 and contained albumin. Granular casts were occasionally present. The patient developed a hemiparesis with convulsions and died in coma. Necropsy revealed a left ventricular hypertrophy, arteriosclerosis and two cerebral hemorrhages. The left kidney weighed 40 gm., the right 112 gm.

Both kidneys were distorted, puckered and shapeless. The capsules were partly adherent and the distortion was marked in these areas. The kidneys were coarse and tough on section. Little apparent distinction was present between the cortex and medulla, but where it could be identified the cortex was atrophied. Microscopically the capsules of the glomeruli in many places were thickened and surrounded by a recent inflammatory infiltration. Some of the glomeruli were only represented by patches of opaque hyalin material. In some places the epithelium seemed healthy but for the most part it was granular. There was a general diffuse increase of interstitial tissue. In parts

20. The case reported by Crooke²¹ would suggest that a chronic nephritis may develop very rapidly (two months) following scarlatina. In this case, however, only one half of that period had elapsed and the pathological picture was very suggestive of an advanced process. The changes in the arteries, and the cardiac hypertrophy would further suggest that in this case the kidney condition antedated the attack of scarlet fever. Such a view, however, would not interfere with the hypothesis that the scarlatina precipitated an acute nephritis that was responsible for the fatal outcome of the case.

21. Crooke, G.: Discussion, *Lancet* 1:1179, 1890.

22. Milligan, W. A.: A Case of Chronic Interstitial Nephritis in a Boy Aged Seven Years, *Rep. Soc. Study Dis. Child.* 2:99, 1902.

23. Guthrie, L.: A Case of Chronic Interstitial Nephritis in a Girl Aged Seven Years, *Rep. Soc. Study Dis. Child.* 1:69, 1900.

of the supporting stroma there were disseminated patches of cellular infiltration supervening on a fibrosis of old standing. The arterioles were patent yet all their coats showed considerable hypertrophy and in some the lumen was almost occluded. The pelvis of the left kidney was dilated, but not the ureter, and there was no obstruction of the latter. Guthrie considered the condition of the kidneys to be a diffuse interstitial nephritis, both of long standing and of apparently recent date.

PATERSON, 1920.²⁴—Girl, aged 7½ years. She was a premature infant and had never thrived. Paterson reported this case with especial reference to the bony changes which were extreme. The wrists were bent from birth. The legs were contracted so that walking was impossible. Though over 7 years of age the height was but 34 inches. The urine contained a trace of albumin but no casts. The phenolsulphonephthalein output was low. Following operation the patient became comatose, developed suppression of the urine and died. The kidneys weighed 45 gm. each. The kidneys were cirrhotic, their capsules stripped with great difficulty and on section several small cystic spaces could be seen. Microscopically, there was a marked increase in fibrous tissues throughout the kidney with a tendency to cyst formation. The tubules were greatly enlarged and filled with colloidal material. The glomeruli were fibrosed in places.

ARRAGA, 1904.²⁵—Boy, aged 9 years. The history of this case was quite typical in that the mother noticed great thirst almost from birth. When about 4 years old the boy began to have attacks of weakness and palpitation on exertion. Headaches became frequent and later almost constant. The polydipsia and polyuria also increased though no volumes were recorded. The patient also suffered from a generalized neuralgia from the time he first walked at the age of 18 months. It was this neuralgia, called rheumatism, that led to his coming under Arraga's care. Slight edema of the ankles developed shortly before admission and the patient died following a 48-hour suppression of urine. No urinalysis was obtained. The necropsy findings other than in the kidneys were not reported.

The kidneys were greatly decreased in volume, weighing 25 gm. The right showed fetal lobulation. The capsule was detached with difficulty leaving a granular surface. The cortex was very much diminished in thickness and the cut surface showed small pinhead cystlike cavities. Histologically, the capsule was thickened with small masses of round celled infiltration among its fibers. The capsules of the glomeruli were thickened, and in some glomeruli the intracapsular space was obliterated. In many glomeruli there was proliferation of the cells of the tuft and in others it was completely converted into a fibrous block with some round cell infiltration. The convoluted tubules showed swelling of the epithelium. Many tubules contained hyalin casts. The loops of Henle had undergone changes similar to those in the convoluted tubules. The arterioles were unchanged for the most part but some showed an obliterative endarteritis.

This case is of interest because of the fact that the mother suffered from malaria during pregnancy and took large doses of quinin during that time. Arraga reports the case as one of congenital malaria but gives no details other than a statement of this parental infection. This circumstance would undoubtedly have to be kept in mind in considering the possible congenital origin of the nephritis.

NAISH, 1912.²⁶—Boy, aged 9½ years. Infantilism was marked, for while this boy was 9½ years old his apparent age was but four. Polydipsia had been

24. Paterson, D. H.: *Proc. Roy. Soc. Med.* **13**:107, 1920 (Case 3).

25. Arraga, A.: *Néphrite interstitielle chez un enfant. Manifestée dès la naissance, mort à neuf ans*, *Arch. de méd. d. Enf.* **7**:285, 1904.

26. Naish, A. E.: *Infantilism with Chronic Interstitial Nephritis*, *Brit. J. Child. Dis.* **9**:337, 1912 (Case 1).

noticed since weaning. The urine was pale and albumin and casts were irregularly found. The boy died in a semi-comatose condition with a partial suppression of urine. Necropsy showed moderate enlargement of the heart.

The kidneys were small, together weighing 31 gm. The surface was irregular but not granular. The capsule was partially adherent. One or two small cysts were present. The cortex was diminished. The glomeruli showed considerable change with thickening of Bowman's capsule and occasional fibrous contracture of the tuft. The convoluted tubules were dilated, especially toward the surface. Some of them formed cysts. The collecting tubules showed little change. The interstitial tissue was greatly increased, and near the surface it was markedly cellular. The arteries were slightly thickened.

GLASER, 1918.²⁷—Girl, aged 10 years. This girl was idiotic, as was also an aunt. The mother died in childbirth of chronic nephritis. A sister died at the age of 2½ years from renal disease. The exact time relationship of these two occurrences to the patient's history was not given. In the reported case polyuria and polydipsia were noted at the age of 15 months. At this time albumin was found in the urine and a diagnosis made of nephritis. The development was greatly retarded both mentally and physically. The mental age when admitted into the clinic was about 3 years and the physical development was not much further advanced. The urine was pale, daily volume, 2,000 c.c.; specific gravity, 1.005, and it contained albumin, 0.25 gm. per liter. Hyalin and granular casts were present. The blood pressure was 100 mm. The arteries were palpable and the heart enlarged. Ophthalmoscopic examination showed albuminuric retinitis. The patient was admitted with diphtheria and died from cardiac failure though there were evidences of impending uremia at the time of death. At necropsy the wall of the left ventricle was thickened and the mitral valve leaflets contained two white plaques. Pulmonary edema, hyperplastic splenitis and enteritis were also found.

Both kidneys were greatly shrunken and the surface was wholly granular. Microscopic examination showed the kidney cortex infiltrated with fibrous scar tissue that was relatively poor in nuclei, hyalin, sclerotic, and of a nodular character. In this scar tissue were atrophic tubules, at times showing evidences of repair. The tubules, in part, were widely dilated and the lumen filled with albuminous material. Well recognized glomeruli were only found in a few areas. Some were completely transformed by scar tissue. Some of the glomeruli were completely destroyed, some showed proliferation of the epithelium. Both in the cortex and in the boundary between cortex and medulla there were many small round cell changes. In the medullary rays the interstitial tissue was diffusely increased, the tubules dilated and the lumina filled with masses of casts. In the larger arteries there was a distinct thickening of the walls while the smaller arteries showed greatly thickened walls with narrowed lumen.

2. Cases of probable chronic diffuse nephritis in which the complete clinical and pathological findings were not reported.

FRÖLICH, 1904.²⁸—Girl, aged 11 months. A sister of the other case reported by Frölich.¹¹ The parents of these children were well but a maternal uncle died of chronic nephritis. This child was apparently well at birth but failed to gain and later developed irregular attacks of vomiting. At the age of 4½ months albumin and casts were found in the urine. The child died from pneumonia at 11 months. (There was no examination of the kidneys but the younger sister showed typical changes.)

27. Glaser, F.: Ueber juvenile primäre Schrumpfnieren, *Jahrb. f. Kinderh.* 87:95, 1918.

28. Frölich, T.: *Norsk. Mag. f. Laegevidensk.* 5:905, 1904 (Case 1).

CHRONIC DIFFUSE NEPHRITIS IN CHILDHOOD. TABULATION

Case	Sex	Age	Family History	General Development	Rachitis	Urinary Findings			
						Polyuria	Specific Gravity	Albumin	Casts
1. Weigert ⁶	6 wks.
2. Democh ⁷	♂	2 mos.	Negative.....	Normal during first month	+	Fatty and hyalin casts
3. Hellendall ¹⁰	♀	6 mos.	Mother and sister had nephritis	Always weak; died of atrophy	Not observed
4. Frölich ²⁸	♀	11 mos.	Uncle and sister had nephritis	Did not gain in weight well	0.6 gm. per L. found at 4½ mos.	Found at 4½ mos.
5. Frölich ¹¹	♀	15 mos.	Uncle and sister had nephritis	Did not gain in weight or do well after first two weeks	Found at 2 wks.	Negative
6. Paterson ¹²	♂	17 mos.	Never took solid food; small and weak; underdeveloped; weight, 10½ lbs.	Extreme rachitis
7. Hellendall ¹³	♀	2 yrs.	Mother and sister had nephritis	Weakly from birth; never walked or talked	Rachitis marked	Drank much especially at night
8. Sawyer ²⁹	♂	2 yrs. 5 mos.	Negative.....	Polyuria and polydypsia 33 oz.	1.002	+	Negative
9. Heubner ¹⁴	3 yrs.	Father had lead poisoning	Was idiotic.....	+	Granular casts
10. Sequeira ³⁰	♂	3 yrs.	Negative.....	Undersized and anemic, weight 16¾ lbs.	Rachitic	Noticed at 8 mos., 20-40 oz.	1.010	Trace	Negative
11. Miller and Parsons ¹⁵	♀	3½ yrs.	Negative.....	Markedly underdeveloped, weight 16 lbs., anemic	Polyuria and polydypsia	1.001-04	Trace	Negative
12. Author's case....	♀	4 yrs.	Did not gain well during the first year	Slightly rachitic	1.018	+	Negative
13. Oppenheim ¹⁶	♂	4 yrs.	Weighed 26 lbs.	Rachitic	Polyuria noticed in early life
14. Morel-Lavelle ³¹ ..	♂	5½ yrs.	Negative.....	Was not well after 18 mos., lost weight	Rachitic	+
15. Barlow ²	♀	5 yrs. 11 mos.	Always weakly and delicate	Noted at 4 years, 3-4 pints	1.010-15	Found only just before death	Negative
16. Miller and Parsons ¹⁷	♀	6 yrs.	Small, backward and underdeveloped, length 36 in.	Polyuria and polydypsia
17. Goodhart ³²	♂	6 yrs.	Cousin similarly affected	Underdeveloped, weighed 31½ lbs.	Polydypsia noted since weaning	1.005	Trace	Negative
18. Parsons ¹⁸	♀	6½ yrs.	Very much underdeveloped	Complaint was "drinking diabetes"	1.010	Trace	Negative
19. Jacobs ¹⁹	♀	7 yrs.	+
20. Milligan ²²	♂	7 yrs.	Weakly from birth, underdeveloped and anemic	Polyuria and micturia 4 pints	1.006	++	Found in terminal stage
21. Guthrie ²³	♀	7 yrs.	Mother had six miscarriages	Was weakly as an infant	1.010	Large amounts in late stage	Occasionally present
22. Paterson ²⁴	♀	7½ yrs.	Negative.....	Premature, bone deformities present from birth, length, 34 in.	Marked rachitis	Trace	Negative
23. Arraga ²⁵	♂	9 yrs.	Mother had malaria during pregnancy	Polyuria noted
24. Naish ²⁶	♂	9½ yrs.	Small and infantile from birth, apparent age 4 years	Late rachitis	Polydypsia noted on weaning	Irregularly present	Irregularly present
25. Förster ³⁴	♂	9½ yrs.	Sister similarly affected, father luetic	Small and underdeveloped, weight 39 lbs.	Polyuria noted at 4½, 2-4 liters	1.004-10	Present in later stages of disease
26. Glaser ²⁷	♀	10 yrs.	Mother had nephritis, sister similarly affected	Very backward idiotic child, mental age 3 yrs.	Polyuria and polydypsia at 15 mos.	1.005	Trace	Present in late stage of disease
27. Goodhart ²⁵	♀	10 yrs.	Was never strong	Marked rachitis	Polyuria and polydypsia from 7 yrs.

—OF THE CLINICAL AND PATHOLOGIC FINDINGS

Weight of Kidneys			Measurement of Kidneys		Manifestations of Uremia	Clinical and Pathologic Evidences of Arteriosclerosis and Hypertension		Cause of Death
Right, Gm.	Left, Gm.	Normal ¹⁸ Gm.	Right, Cm.	Left, Cm.		Blood Vessels	Heart	
....	13.0	1.7×1.0×0.5	2.0×1.1×0.4	Right ventricle hypertrophied, congenital defect	Congenital defect in the heart
....	15.0	5.0×3.0×2.5	5.0×3.0×2.5	Slight microscopic thickening of renal arterioles	Enlarged clinically, hypertrophied and dilated	Pulmonary edema, bronchopneumonia
4.0	4.0	20.0	3.3×2.0×0.6	3.3×2.0×0.6	Negative.....	Bronchopneumonia and atrophy
....	30.0	Had irregular attacks of vomiting	Pneumonia
18.0	17.0	30.0	Had periodic attacks of vomiting	Atheromatous changes in aorta	Hypertrophy of left ventricle	Pneumonia
27.0	27.0	36.4	Died in uremia.....	Thickening of renal arterioles	Negative.....	Uremia
6.0	6.0	38.4	4.0×2.5×0.7	4.0×2.5×0.7	Had periodic attacks of vomiting	Negative.....	Atrophy, bronchopneumonia
24.0	24.0	50.0	Had "fits" and vomiting spells, died in uremia	Negative.....	Uremia
....	50.0
....	50.0	Apparently died in uremia	Slight hypertrophy of left ventricle	Uremia
30.0	30.0	50.0	Slight hypertrophy of left ventricle
17.0	19.0	56.0	4.0×2.5×1.0	4.0×2.5×1.0	Died in convulsions	Slight atheromatous changes in aorta	Enlarged clinically, left ventricle hypertrophied	Uremia
43.7	48.6	56.0	7.0×3.5×2.5	7.5×3.0×2.5	Had periodic attacks of vomiting, died in uremia	Had headaches and dimness of vision, renal arterioles slightly thickened	Negative.....	Uremia
....	59.0	Atrophic cirrhosis of liver
13.7	23.0	59.0	5.0×3.7×1.2	5.6×3.5×1.5	Died in convulsions	Showed sclerosis of renal arterioles	Heart hypertrophied	Died in convulsions
Comb. Wt. 32.0	124.9	4.3×3.0×—	4.75×3.0×—	Died in uremia.....	Renal arterioles slightly thickened	Slightly hypertrophied	Uremia
....	59.0	Had recurrent attacks of "tetany" and vomiting	Renal vessels thickened	Hypertrophied and dilated	Died in convulsions
Comb. Wt. 30.0	133.6	Renal vessels thickened	Enlarged clinically, heart hypertrophied	Bronchopneumonia
29.0	27.0	67.0	5.5×4.4×2.2	5.1×3.2×2.2	Smaller arterioles thickened	Heart hypertrophied	Bronchopneumonia
....	65.0	Headaches and albuminuric retinitis present, renal vessels thickened	Enlarged clinically, hypertrophied with dilatation	Cardiac failure
112.0	40.0	65.0	Died in coma.....	Arteries palpable, two cerebral hemorrhages	Enlarged clinically, left ventricle hypertrophied	Died in coma
45.0	45.0	65.0	Died in uremia following operation	Uremia
25.0	25.0	78.0	Suppression of urine preceded death	Had attacks of dyspnea and palpitation, obliterative endarteritis
Comb. Wt. 31.0	156.0	Died in coma with suppression of urine	Hypertrophy of heart	Died in coma
....	78.0	Cerebral vessels sclerosed	Heart hypertrophied
....	81.0	Albuminuric retinitis, arteries thickened	Enlarged clinically, left ventricle hypertrophied	Diphtheria, cardiac failure
....	86.0	2.9×3.0×—	2.9×3.0×—	Died in uremia.....	Left ventricle slightly hypertrophied	Uremia

SAWYER, 1903.²⁹—Boy, aged 2 years and 5 months. This baby developed "fits" at the age of 7 weeks though no history of any specific fever was obtainable. He habitually suffered from polyuria and was thirsty in addition. He vomited occasionally. He was rachitic and undersized (weight, 15½ pounds). The urine had a specific gravity of 1.002 and contained a trace of albumin but no casts. The average daily volume was 33 ounces. He finally developed uremia and died in coma. No hypertrophy of the heart was present.

The kidneys were small, weighing 24 gm. each. The surface was irregular and the renal tissue was greatly decreased. The left renal pelvis was slightly dilated. Microscopically, there was considerable fibroid overgrowth with marked absorption of the pyramids and destruction of the epithelium. Bowman's capsule was thickened in most instances. (The pathologic description in this case is not complete.)

SEQUEIRA, 1900.³⁰—Boy, aged 3 years. Polyuria was first noted at 8 months, following whooping cough. The child was underdeveloped, rachitic and markedly anemic. The weight on admission to the hospital was 16¾ pounds. The retinae showed no signs of albuminuric involvement. The urinary volume was large, from 20 to 40 ounces daily. The specific gravity was 1.010 and a trace of albumin but no casts were found. The child gradually became comatose, and apparently died in uremia. There was some hypertrophy of the left ventricle. The kidneys were large and granular showing cirrhotic changes on microscopical section. (The pathologic discussion of the kidneys in this case is inadequate for accurate diagnosis of the lesion present.)

MOREL-LAVALLEÉ, 1885.³¹—Boy, aged 5½ years. He had complained of swelling of the abdomen from the age of 18 months. Examination showed a rachitic infant with marked ascites. Paracentesis was performed three times before death. Albumin was present in the urine the last few days of life. Necropsy disclosed a bronchopneumonia, atrophic cirrhosis of the liver, an enlarged fibrous spleen and cirrhotic kidneys.

The kidneys had an essentially normal gross appearance. Microscopically there was sclerosis around the glomeruli with capsular involvement. The tubules were healthy in some areas but in others they were dilated, the epithelium desquamated, and the lumen of the tubule filled with granular detritus or casts. The principle lesion was the increase in the interstitial tissue.

(The determining factor in the clinical picture of this case was the cirrhosis of the liver. The same is probably true of the pathological picture and the changes in the kidney can hardly be called primary. While this case has been included by Oppenheim³² and others in their tabulations, it seems better to follow the example of Glaser²⁷ and eliminate it from the series of accepted cases.)

GOODHART, 1890.³²—Boy, aged 6 years. This infant was bottle fed and intense thirst was noted at the time of weaning from the bottle. When 3 years old he had an attack of fever and vomiting of unknown etiology. After that he had periodic attacks of tetany and of vomiting. The urine was regularly of low specific gravity with traces of albumin irregularly present.

29. Sawyer, J. E.: Chronic Interstitial Nephritis in Children, Birmingham M. Rev. **54**:511, 1903 (Case 4).

30. Sequeira, J. H.: A Case of Polyuria in a Child Aged Three Years, Rep. Soc. Study Dis. Child. **1**:17, 1900.

31. Morel-Lavallée, M.: Cirrhose atrophique du foie, de la rate et des reins chez un enfant de cinq ans-autopsie. Rev. mens. de malad. d. l'enf. **3**:166, 1885; abstr. in Jahrb. f. Kinderh. **23**:459, 1885.

32. Goodhart, J. F.: Acute and Chronic Bright's Disease, Cyclopedia of the Diseases of Children (Keating), Phila. **3**:541, 1890.

He was greatly underdeveloped and when seen at the age of 6 weighed but 31½ pounds. Urine had a specific gravity of 1.005 and contained a trace of albumin but no casts. There was no edema. Died in one of the recurrent attacks of tetany. The heart was large but flabby and dilated.

Both kidneys were small and shriveled, the capsules adherent, the surface pale, the cortex diminished and the pelvis a little dilated. There was a large excess of fibrous tissue in the cortex and many of the glomeruli were shrunken and hyalin. The vessels were thick. (This case is reported by Goodhart as a parenchymatous nephritis with the added note that it was a very perplexing case. The reported data are entirely compatible with the presence of a chronic diffuse nephritis, but the discussion of the pathological changes in the kidney is too brief to permit of a definite and final determination of the renal lesion. Goodhart also reports a cousin of this boy who presented essentially the same clinical picture but who did not come to necropsy.)

GULL AND SUTTON, 1872.³³—Girl, aged 9 years. Among their case reports Gull and Sutton include a description of the kidneys of a nine year old girl in whom there was left ventricular hypertrophy and dilatation. "The kidneys were very much smaller than natural especially the left; one weighed 2 ounces, the other 1½ ounces. The kidneys in consequence of being greatly contracted were much out of shape; their surfaces were irregular and puckered, not finely granular." "The arterioles of the kidneys were much thickened by fibroid change." (This case is of interest because it apparently is the first description of the kidneys from a case of chronic nephritis in childhood. The clinical history was not given.)

FÖRSTER, 1887.³⁴—Boy, aged 9½ years. This boy was thirsty from early life and at the age of 4½ polyuria became prominent with the excretion of two to four liters of urine daily. The specific gravity varied from 1.004 to 1.010. Albumin was found only during the latter part of his illness. He was markedly underdeveloped and at the age of 9 weighed but 39 pounds. He died after a week of increasing lassitude, and tiredness, etc.

Necropsy showed the presence of sclerotic changes in the brain, cardiac hypertrophy and contracted kidneys. A sister died at 8¼ after a similar clinical course, but no postmortem examination was made. In this case the father was syphilitic. (The kidney pathology was not studied or reported microscopically.)

GOODHART, 1890.³⁵—Girl, aged 10 years. A small girl with marked rachitic deformity. She had never been strong and her legs had been crooked since she first began to walk. Polyuria and polydipsia had been noted for two years prior to admission, and more recently headaches, dyspnea and coma. She was admitted to the hospital in coma and died in a convulsion twenty-four hours later. The left ventricle was somewhat thickened.

The kidneys were very small, 2.8 x 3.0 cm. They were firm and pale, the capsule adherent and the surface granular. Hardly any of the cortex remained. The section showed copious nuclear growth and not mere fibrosis with atrophy. Thick irregular bands of highly nucleated material spread from the cortex downward to the medulla and within them were thickened and shriveled capsules and wasted tubes. They had a basis of fibroid material and showed well marked puckering or cicatrization. Outside them were tracts of comparatively healthy tubes. (The pathologic picture lacks definitiveness.)

3. Cases of chronic diffuse nephritis in children over 10 years of age.

33. Gull, Sir W. W., and Sutton, H. G.: *Med. Chir. Tr.* **55**:301, 1872 (Case 8).

34. Förster, R.: *Ueber Schrumpfnieren im Kindesalter*, *Jahrb. f. Kinderh.* **26**:38, 1887.

35. Goodhart, J. F.: *Cyclopedia of the Diseases of Children* (Keating) **3**:556, 1872.

FILATOFF AND RACHMANINOFF, 1883.³⁶—Girl, aged 12 years. This girl was weakly from birth and during childhood suffered from urinary frequency and later cardiac palpitation. At the age of eleven she had a left sided hemiplegia. She complained of headache and dimness of vision. Albuminuric retinitis was found on ophthalmoscopic examination. She was apathetic and showed marked anemia. No edema was present. Postmortem examination showed "granular atrophy of the kidney" with a left sided cardiac hypertrophy, chronic endarteritis, and old cerebral hemorrhage. (This case is available in the German abstract only, so the full details of the renal pathology cannot be discussed.)

BRILL AND LIBMAN, 1899.³⁷—Girl, aged 14 years. The family history is quite complicated in this case. There were twelve children. Six of these died in early life, causes unknown. Of the remaining six, four presented the clinical picture of chronic interstitial nephritis. The patient was always weak and undersized. Edema developed a year previous to admission and was present for a short time. Following a severe fright she developed a left-sided hemiplegia. At that time the urine had a specific gravity of 1.010 with 1.4 gm. of albumin per liter. Both hyalin and granular casts were present. Ophthalmoscopic examination showed albuminuric retinitis. Death followed pneumonia and pulmonary edema. In addition there was cardiac hypertrophy, general chronic arteritis, cerebral hemorrhage and hemorrhages in the lungs, spleen and mesentery found at necropsy.

The kidneys were small, measuring $2.0 \times 4 \times 3.0$ and $6.25 \times 3.5 \times 2.5$ cm., respectively, and weighing 59 and 34.5 gm., respectively. The capsules were adherent and the surface granular. The cortex was greatly narrowed. The pelves of both kidneys were greatly enlarged. Microscopically, the right kidney showed a marked chronic interstitial nephritis with complete replacement of the renal parenchyma with fibrous tissue in some areas. Many of the glomeruli were converted into fibrous balls. Some of the tubules were dilated, others atrophied with marked degeneration of the epithelium. The arteries showed obliterative endarteritis and many were completely closed. The left kidney showed essentially the same changes as the right. Both kidneys presented the signs of chronic congestion and scattered through them were many small areas of calcification similar to like areas occurring in the liver.

DISCUSSION OF THE CLINICAL FINDINGS

The reported cases show a remarkable similarity in their clinical manifestations, though these latter show variations dependent on the age of the patient and the severity of the symptoms as well as on the individual viewpoints of the different authors. These lesser diversities serve to emphasize rather than to detract from the essential similarity. In all cases the outstanding causal factor seems to be a severe and progressive diminution in the functional activity of the kidney.

Evidences of nutritional disturbances in early infancy, often very severe, were almost universally noted. As a rule, they did not make their appearance until weaning, or the latter part of the first year in life, though in the cases of Miller and Parsons,¹⁵ Milligan,²² and

36. Filatoff, N. and Rachmaninoff, J.: Ein Fall von primärer Nierenschwundung und atheromat. Degeneration der Arterien bei einem 12 jährigen Knaben. *Jahrb. f. Kinderh.* 20:209, 1883.

37. Brill, N. E., and Libman, E.: A Contribution to the Subjects of Chronic Interstitial Nephritis and Arteritis in the Young and Family Nephritis; with a Note on Calcification in the Liver, *J. Exper. M.* 4:541, 1899.

Naish,²⁶ the symptoms dated from birth itself. In my case the history indicated that the feeding was difficult and that the child did not do well during the first year of life. The feeding becomes progressively more difficult with weaning and change to a solid diet. The boy of Paterson¹² refused solid food up to the time of death at 21 months. Oppenheim¹⁶ also reported a case in which the refusal to eat and consequent loss in weight undoubtedly were factors in the final development of uremic acidosis and death. The explanation of this self limitation in diet is not clear but the presence of a severe type of nutritional disturbance in these patients is unquestionable.

These children apart from refusal to eat showed marked backwardness in their physical development. Many were markedly undersize and underweight and nearly all were described as "weakly" or "delicate." Mental as well as physical retardation was present though the mental retardation was the less marked. The children described by Heubner¹⁴ and Glaser²⁷ were idiotic, but for both an etiology of the idiocy other than renal was present.

In addition to being undersized and backward in physical development many of these children had pronounced bony deformities. The children reported by Oppenheim¹⁶ and Paterson²⁴ in particular showed extensive skeletal deformities developing during the first year of life. This backwardness in development and the associated deformities have been especially emphasized by the English writers under the name of "renal infantilism" or "renal dwarfism." This literature has recently been summarized by Paterson.¹² He pays especial attention to the extensive bony changes found and thinks them nutritional in origin but he does not consider the changes to be completely identical with those in true rachitis. Rachitis is usually recognized as being nutritional in origin. The recent work of McCollum, Simmonds, Shipley and Park³⁸ has indicated that it may be caused by a disturbance in the balance of inorganic salts in the diet when combined with an insufficiency of an organic factor. The blood of rachitic children has also been shown to contain a normal or slightly lowered amount of calcium while the inorganic phosphates are markedly reduced in quantity.³⁹

Barber,⁴⁰ in particular, has reported several cases and emphasized the occurrence in older children of a variety of late rachitis that is associated with a chronic interstitial nephritis. It is this type of case in particular that he classifies under the name of "renal dwarfism."

38. McCollum, E. V., Simmonds, N., Shipley, P. G. and Park, E. A.: Studies in Experimental Rickets. VIII. The Production of Rickets by Diets Low in Phosphorus and Fat-Soluble A, *J. Biol. Chem.* **47**:507, 1921.

39. Howland, J. and Kramer, B.: Calcium and Phosphorus in the Serum in Relation to Rachitis, *Am. J. Dis. Child.* **22**:105, 1921.

40. Barber, H.: Renal Dwarfism, *Quart. J. Med.* **14**:205, 1921.

Barber's cases were striking because they all were in older children. These children were often backward in development during childhood but it was not until the age of from 10 to 15, apparently at about the onset of puberty, that rachitic changes appeared. Genu valgum was the preponderant lesion in all. The etiology of this condition is obscure and its complete identity with the condition seen in younger children has still to be proved.

Pallor and anemia is a well recognized accompaniment of chronic nephritis in childhood but accurate blood studies are lacking in these cases. Anemia is present in practically all cases of rachitis and is also a characteristic feature of chronic diffuse nephritis in adults. Apparently the renal insufficiency in these cases is responsible for a general nutritional disturbance which leads to the development of a severe secondary anemia, but further study is desirable in order to establish the exact etiology of this anemia.

Miller and Parsons¹⁵ pointed out the similarity between the clinical pictures in "renal infantilism" and in some cases of diabetes insipidus. They think that the condition of the child with chronic nephritis may, in part, be due to the general disturbance in nutrition but this last in turn is dependent on the drain put upon the system by the long continued polyuria and albuminuria.

It is true that the polyuria does not reach the extreme degree seen in cases of diabetes insipidus but undoubtedly it is one of the earliest and best marked symptoms of chronic infantile nephritis. The immediate symptom may be any one of the different after effects of an increased water metabolism. Great thirst and consequent drinking of large quantities of water is common and may be recognized as soon as weaning occurs, as in the case of Arraga²⁵ or Naish.²⁶ It is possible that the increased intake of fluids fails to attract the attention and the increased output is first observed as either nocturia, enuresis or polyuria. In the case of Parsons¹⁸ the complaint was "drinking diabetes."

The examination of the urine reveals essentially the same characteristics as those found in chronic diffuse nephritis in adults, and indicates a relative severe degree of kidney damage. As has been mentioned above, the volume of the urine is large, it is pale, acid, and the specific gravity is low. The specific gravity varies between 1.001 and 1.018, though this last represents a terminal value in my case.

In all these cases albumin was present in variable though always in relatively small amounts. In general, the quantity of albumin is very low while the child is fairly well and it occasionally may even be absent. The amount is increased during uremic attacks or in the terminal stage of the condition. The quantity of the albumin, however, does not furnish a reliable guide to the prognosis. Casts were of relatively infrequent occurrence though they occasionally were present.

They were certainly more common in the terminal stages of the nephritis. At this time both hyalin and granular casts may be found though they were absent in the author's case.

In the case of Paterson²⁴ the phenolsulphonophthalein excretion was found to be markedly lowered. The newer methods of studying renal function have only recently been applied to children. This case of Paterson's was the only one in the present series in which functional studies were made. The clinical evidence indicates the presence of an extreme degree of renal insufficiency but this should be confirmed by exact chemical methods. Such studies are of particular value in the differential diagnosis between this condition and the clinically similar diabetes insipidus.

Edema was of relatively infrequent occurrence and was only observed in six instances. In the majority of these cases the edema was terminal and was associated with cardiac failure rather than with the renal disturbance.

Chronic diffuse nephritis in adults presents a definite picture of cardiovascular as well as of renal change. In this hypertensive type of adult nephritis the urinary findings correspond very closely to those seen in children with chronic diffuse nephritis.

The cardiovascular system of these children then is worthy of especial note because of possible light that it may throw on the more complicated problems of adult medicine. Of thirteen children under 5 years of age only five showed evidences at necropsy of cardiac hypertrophy. This hypertrophy in most cases was slight and involved only the left ventricle. In one of these five cases (my own) there were slight arteriosclerotic patches on the mitral valve together with slight thickening of the aortic cusps. In the other seven cases the heart and blood vessels were apparently normal, both on macroscopic and histologic examination. Microscopic examination of the kidneys in nearly all these cases revealed the presence of some change in the walls of the renal arterioles, but this change was usually limited to a slight adventitial thickening.

A slightly different picture is presented in the cases reported of children between 5 and 10 years of age. Out of eleven such cases there are only four in which there was no cardiac hypertrophy. The other cases all showed more or less hypertrophy either of the left ventricle or else of the heart as a whole. The other seven children presented more extensive changes. In the child reported by Glaser²⁷ definite atheromatous patches were present on the mitral valves, and the brachial arteries were thickened and palpable, as in the girl described by Guthrie.²³

Both these children complained of dimness of vision and in both an ophthalmoscopic examination revealed the presence of a typical

albuminuric retinitis. Dimness of vision was also complained of by the boy reported on by Oppenheim¹⁶ but the eye grounds were not examined. The girl seen by Guthrie²³ had a left sided hemiplegia, and two old cerebral hemorrhages were discovered at necropsy, as in the final stage in adult hypertension. The cases of Filatoff and Rachmaninoff³⁶ and of Brill and Libman³⁷ also might be included in this series of cases by extending the age limit a few years. Both these children, aged 12 and 14 years, respectively, had cardiac hypertrophy, generalized arteriosclerosis and hemiplegia.

Other less well defined symptoms of hypertension, such as headache, vertigo, nausea and vomiting, dyspnea on exertion, palpitation and angina, are mentioned in the different reports but do not appear with any degree of regularity. In the greater number of these cases there was no record of blood pressure estimation, so that there is no direct evidence available as to the degree of hypertension pressure. From a comparative point of view it may be said that the chronic nephritis of congenital origin in childhood presents essentially the same clinical picture as that of primary chronic diffuse nephritis in the adult, with the difference that the nutritional disturbance is more marked in the infant and cardiovascular or hypertensive phenomena are less striking than in the adult. In fact, these children very definitely seem to show a direct correlation between age and the extent of the cardiovascular change. The same correlation between the age and the severity of the renal lesion is not observed. Quite as extensive a fibrosis of the kidney was found in the younger children without cardiac hypertrophy as in the older children with marked arteriosclerosis. This observation unquestionably leads to the conclusion that the renal lesion is primary while the cardiac hypertrophy and the arteriosclerotic changes are secondary.

Uremia was present in nearly all the cases studied. In six cases there was a history of periodic attacks of vomiting or convulsions that were evidently uremic in origin. In the majority of instances the uremia was a terminal condition. Oppenheim¹⁶ and Paterson¹² both reported cases in which starvation acidosis undoubtedly was a factor in the development of the uremia. Barber⁴⁰ and Paterson²⁴ have also pointed out the danger of uremia as a postoperative complication in these cases. The importance of the newer chemical methods for the study of renal function should be emphasized, both from the standpoint of diagnosis and of recognition of impending uremia. My patient was admitted to the hospital in convulsions with a diagnosis of lethargic encephalitis. The child was in extremis at the time and it was the urinary findings alone that made possible clinical recognition of the condition.

In the majority of these cases death was due to uremia. The weakness and debility of these patients are important, however, for next to uremia, bronchopneumonia is the most frequent cause of death.

DISCUSSION OF THE PATHOLOGICAL PICTURE

The pathologic picture in these different cases was remarkably uniform. The kidneys were small, pale and atrophic and about equally affected. In some instances one kidney showed slightly more marked changes than the other but the difference was always one of degree rather than kind and never extreme. The capsule was slightly adherent though it stripped fairly readily, leaving a roughened granular surface. In the more advanced cases there was definite scarring of the kidney surface as well.

On section the cut surface was pale, yellowish red and showed marked atrophy of the cortex which was only from 2 to 4 mm. in thickness. Small pinhead sized cysts were present in some cases but they were isolated and indicated no relation to the changes found in congenital cystic kidney.

Microscopically, the glomeruli showed extensive change, depending on the degree of kidney damage. In the less affected kidneys, or in the less affected areas of a single kidney, they were enlarged and hypertrophied. Others showed a connective tissue infiltration around the glomeruli that led first to fusion of the different loops comprising the tuft, or to adhesions between the tuft and the capsule. This led to a final condition of atrophy of the glomeruli with subsequent hyalin change.

The tubules showed swelling and degenerative changes in their epithelium. In many cases the epithelium was desquamated and the lumen of the tubule filled with cellular detritus. Granular and hyalin casts were also present in varying amounts. The condition of the tubules varied greatly in the different cases reported. In the majority of instances both atrophy and dilatation were present in different parts of the section. In other cases either atrophy or dilatation of the tubules was the predominating condition. In the new case reported here the tubules for the most part were distorted or obliterated by scarring and cellular infiltration, but dilated tubules could be found throughout the section.

I have pointed out the importance in renal pathology of the study of the tubule as a whole.⁴¹ Sections permit careful investigation of the component parts of the tubule but fail to give the relationship between these parts. In the present instance the tubules were dissected free

41. Greene, C. H.: Bilateral, Hypoplastic, Cystic Kidneys, to be published.

after maceration of the kidney in concentrated hydrochloric acid. The contracted condition of the glomeruli was striking but there was no change in the architecture of the tubule as a whole. The difference is marked in this respect between this condition and the clinically similar hyoplastic cystic kidney.⁴¹

Increase in the interstitial connective tissue was uniformly present in all cases, though very variable in amount. It was usually present as a diffuse infiltration of fibrous tissue but clumps of round cells were present in many of the cases. Thickening was likewise present in the walls of the smaller arterioles and in the older children the vascular change suggested an obliterative endarteritis.

ETIOLOGY OF THE KIDNEY LESIONS

The etiology of this condition is not clear. Scarlatina is the prime cause of acute nephritis in childhood and this may later become chronic. In the series of cases discussed, however, there was no history of scarlet fever and in most instances a specific statement as to its absence. The case of Jacobs¹⁹ was an exception, but it seems probable that the chronic nephritis in this case antedated the attack of scarlatina. Measles was the only acute illness noted with any frequency, but measles was by no means uniformly present and is known to be a very infrequent cause of nephritis.⁴²

The most striking feature in many of these case histories was the report that the child was delicate from birth. In nearly every instance the child was weak and sickly, and more or less backward in development. Even with the marked frequency of malnutrition in children, the universal presence in all these children of a severe grade of nutritional disturbance would seem to indicate an underlying cause other than simple malfeeding. A chronic nephritis, of greater or less severity, existing at birth could well be the cause of such a nutritional upset. Three of the children were less than 1 year old, and the patient of Wiegert⁶ died at the age of 6 weeks. An acute nephritis may exist at birth, for Karsner⁴⁴ has reported one case and collected three more from the literature. These cases were all rapidly fatal. That any such infection should occur and then develop into a chronic nephritis similar to those cases here discussed is not likely, and that it should do so without observable symptoms is even less probable. It would seem,

42. Aronade⁴³ has presented a case of acute nephritis following measles in a girl aged 5 and this later developed into a chronic kidney lesion but the clinical course and behavior of the patient was entirely distinct from the present series.

43. Aronade, O.: Ueber chronische Nephritis im Kindesalter, *Jahrb. f. Kinderh.* **69**:652, 1909.

44. Karsner, H. T.: Congenital Nephritis, *New York M. J.* **88**:1076, 1908.

therefore, that the kidney lesion in these cases was not only primary in nature but congenital in origin as well.

While the congenital nature of this type of lesion is recognized, the underlying cause is by no means clear. The first thought is of a hereditary or familial defect in the kidney. In a number of instances families have been reported in which the adult members of two or more generations suffered from chronic nephritis.⁴⁵ Inasmuch as the late development of the nephritis in these latter cases raises doubts as to its congenital origin, they will not be discussed here. In the majority of the cases studied the family history was either noncommittal or else entirely negative as to familial nephritis but this was not true in all. The two children reported by Förster³⁴ were brother and sister. The parents of the two children studied by Frölich⁴¹ were apparently healthy, but a maternal uncle had died of chronic nephritis. The children discussed by Barber⁴⁶ were likewise brother and sister. They were the result of the seventh and eighth pregnancies and it was noted that the mother was not well during either pregnancy. It is a peculiar coincidence that the two sisters reported by Hellendall¹⁰ were also the result of the seventh and eighth pregnancies. About the fourth month of the seventh pregnancy the mother, who had previously been well, noticed swelling of the feet and was said to have later developed symptoms of chronic nephritis. During the eighth pregnancy these same symptoms recurred in a more severe form. In the report of Glaser²⁷ it was stated that the mother of the patient died during childbirth of chronic renal disease, and that a sister died at the age of 2½ years from a malady similar to that of the patient. In this group of cases there is evidence to indicate a familial origin of the disease.

In some of the remaining cases the presence of congenital or developmental defects indicated that the kidney lesion possibly was part of a larger process. The child reported on by Weigert⁶ had a congenital malformation of the heart. The girl reported on by Glaser²⁷ was idiotic, as was the child discussed by Heubner.¹⁴ The father of this latter infant was a sufferer from lead poisoning. This has been known to affect the parental germ plasm with the production of developmental defects in the offspring.⁴⁷ The chondromas present in the kidney of the younger of the two infants described by Hellendall¹⁰ may also be looked on as evidences of congenital defects of development.

45. Kidd, J.: The Inheritance of Bright's Disease of the Kidney, *Practitioner* **29**:104, 1882.

46. Barber, H.: Chronic Interstitial Nephritis in Children, *Brit. M. J.* **2**:1204, 1913.

47. Ballantyne, J. W.: Manual of Antenatal Pathology and Hygiene, The Foetus, Edinburgh, 1902, p. 258.

Recently ⁴¹ I reported a case of bilateral hypoplastic cystic kidneys. This child presented the characteristic clinical picture of chronic diffuse nephritis. Urine examination showed the presence of a marked renal insufficiency of the type found in chronic diffuse nephritis. This would indicate that it was the functional rather than the morphologic changes in the kidneys that determined the symptomatology of the disease. The microscopic appearance of the sections in this case of congenital defect in the development of the kidney corresponds very closely with the appearance of the illustrations of the kidney published by Paterson.²⁴ It is possible that the case of Paterson and perhaps others from this series were cases of defective development of the kidney rather than of diffuse nephritis.

The boy reported on by Arraga ²⁵ was born of a mother suffering from malaria and taking quinin throughout pregnancy. Furthermore, it should be noted in the reports cited above, especially those of Hellendall ¹⁰ and Barber ⁴⁶ that the affected children were born of mothers who suffered from renal disorders during pregnancy. It is possible, then, that these cases while congenital were not familial in origin but rather represented the results of maternal intoxications.

Sawyer ⁴ and Guthrie ²³ in particular have advanced the idea that this condition was syphilitic in origin. It is true that the mother of the child reported by Guthrie had six miscarriages and that the father of the children described by Förster ³⁴ died of syphilis. With these exceptions syphilis either was not mentioned in the clinical reports or else there was a specific statement as to its absence. In view of our present day knowledge of congenital syphilis, this condition can be ruled out as an etiologic agent in this series of cases.

Glaser ²⁷ suggested the possibility of a primary renal vascular hypoplasia as underlying the pathologic changes. In this connection it should again be pointed out that in the younger children the vascular changes were relatively slight. The renal vessels were reported as being only slightly thickened if at all, and there was no evidence of general arteriosclerosis or cardiac hypertrophy. In my case there was a slightly hypertrophied left ventricle and the mitral valve contained two thickened plaques. The renal vessels showed only slight changes on microscopic examination. In the children over 5 the cardiovascular changes became progressively more prominent. Cerebral hemorrhage occurred in the case discussed by Guthrie ²³ and in the somewhat older children reported by Filatoff and Rachmaninoff ³⁶ and Brill and Libman.³⁷ A lesser degree of vascular change and cardiac hypertrophy was present in others of the older children. If cerebral hemorrhages may be taken as an indication of the presence of a severe degree of cardiovascular sclerosis with hypertension, then it is noteworthy that these changes were present only in older children

in which there had been time for the vascular changes to appear. Though not entirely conclusive it would seem as if the primary lesion in the kidney was renal and not vascular in origin.

In the other cases reported no clue as to the origin of the lesion was found. Until more is known of the pathology of fetal development any assignment of a cause for this condition would seem to be largely a matter of individual opinion and choice.

SUMMARY

A careful study of the reported cases of chronic nephritis in childhood indicates that chronic diffuse nephritis is a distinct clinicopathologic entity of probable congenital origin though no definite etiology may be ascribed.

It is characterized by evidences of functional insufficiency of the kidneys dating from early infancy. Children so affected show great developmental disturbance with associated stunting and backwardness in growth, difficulty in feeding, anemia and rachitis. The renal insufficiency is more directly evidenced by the excretion of large volumes of dilute urine with a low specific gravity. This urine contains a slight amount of albumin and casts are present in small numbers. In those cases in which it has been determined the phenolsulphonephthalein excretion is low. Death usually results from uremia. The pathologic picture in these cases is similar to, if not identical, with the chronic diffuse nephritis of adults.

48. Vierordt, H.: *Anatomische, physiologische, und physikalische Daten und Tabellen*, Jena, 36, 1906.

THE ANTISCORBUTIC PROPERTY OF FRUITS

II. AN EXPERIMENTAL STUDY OF APPLES AND BANANAS *

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AND

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With the termination of the world war there appears to be an end also of the work of the majority of agencies formed to advocate the conservation of foods. Such a course should not be pursued as it is undoubtedly a mistake from a financial standpoint and possibly from a physiologic one. The result of the present economic situation may be a limited food supply for the people of certain sections of this country. Such a condition of affairs could be prevented to some extent, or, at any rate, alleviated by a general conservation of foodstuffs throughout the nation. We are not unmindful of the prevalence in some states of pellagra and a predicted increase of this disease due to certain food shortages. Nor can we ignore the possibility of other deficiency diseases following in the wake of such a condition.

Desiccation is one of the most important processes advocated for preserving foods. This method is applicable to both vegetables and fruits, particularly those of a perishable nature. However, this procedure, or any other involving the subjection of foods to special treatments, should not yield a product unsatisfactory from a nutritional standpoint. That the original material has not been rendered unsuitable for human consumption can be proven only by scientific evidence of a physiologic nature. We have already published data regarding the effect of desiccation on the antiscorbutic potency of a number of foodstuffs. This communication deals with the effect of this treatment on apples and bananas. The sum total of our experiments has convinced us that if due cognizance is to be taken of the antiscorbutic value of foods, then each foodstuff must be studied individually both in its original and its preserved form.

It has been known for a long time that fresh vegetables and fruits will prevent or cure scurvy, as the case may be. Any standard textbook on children's diseases contains a definite list of antiscorbutic

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* The experiments reported herein were completed in June, 1919, but circumstances have prevented our detailing the work sooner. A preliminary report was given before the Society for Experimental Biology and Medicine, Proc. 18:1921.

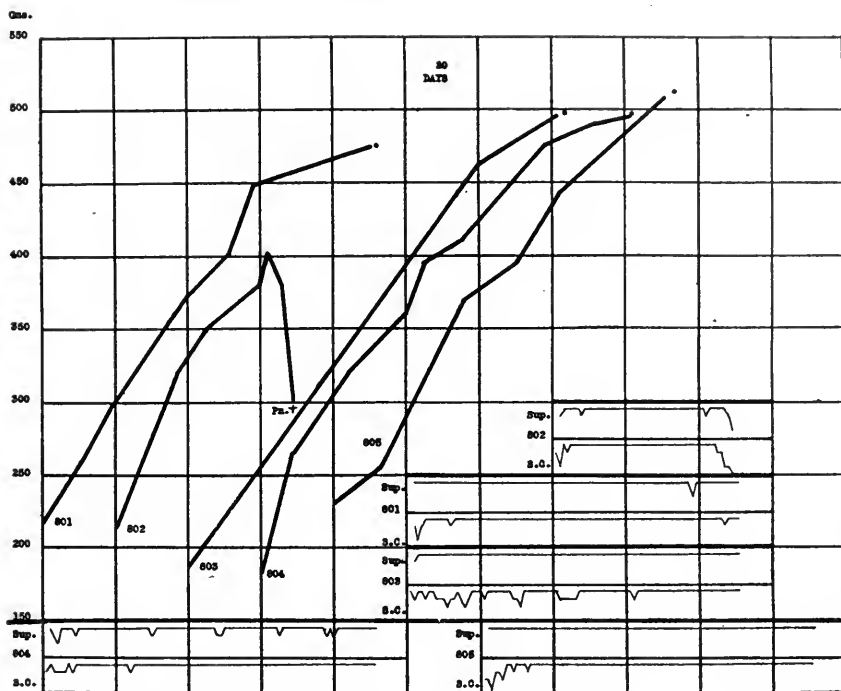


Chart 1.—This group of guinea-pigs shows the result of supplementing a basal diet deficient in the antiscorbutic vitamin but otherwise adequate, with 10 gm. fresh bananas per animal daily. With the one exception, animal 802, which died of pneumonia on the fifteenth day without showing signs of scurvy, all the guinea-pigs increased in weight up to 100 days when the experiment was discontinued. The antiscorbutic vitamin is thus shown to be present in bananas.

NOTE: The following key is applicable to all the charts:— Sup.=Supplemental intake. S. C.=Basal Soy cake diet. An.=Anesthetized. Pn.=Pneumonia. S.=Scurvy. Pn. S.=Pneumonia with Scurvy. Pn. S? =Pneumonia with questionable scurvy. OK.=Animal apparently recovered. *=Termination of the experiment. †=Death. Per.=Perforated stomach. The growth curves, which are self-explanatory, are separated from the feeding curves by a large heavy base line which extends out to the left under the weight figures. The feeding curves, always at the bottom of the chart, are plotted on a basis of 4. In these curves there are five equal subdivisions between the base lines. Consequently if an animal were eating all his food the curves of supplemental and basal intakes would be parallel to the base lines four-fifths of the distance above them. The number of the animal to which the feeding curves belong is always placed on the left opposite the base line separating the curve of supplemental intake (Sup.) from that of the intake of the basal diet (S. C.). The curve of the supplemental intake is always above that of the basal food intake. The time relation is the same for all curves; that is, twenty days to each square.

As an example of the food curves, take No. 801, Chart I. This animal consumed all of his supplemental intake on every day except on the seventy-eighth day, when he ate only one half of it. Of the basal diet, he ate on the first day, three fourths; on the second day, one fourth; on the third day, three fourths; on the fourth day, all; and all on every day thereafter except on the twelfth and eighty-seventh days when he consumed only three fourths of the basal diet.

foods. For example, in Pfaundler and Schlossmann¹ we find the following advice:

In place of the food which has heretofore been given, the child should receive fresh, at most briefly heated, or still better raw, cow's milk, if such is to be had from a reliable source. Besides this two to four teaspoonfuls per day of raw meat juice should be given, and the same amount of fresh fruit juice (obtained according to the season of the year from oranges, grapes, lemons, cherries, currants, blackberries, apples, pears, apricots, huckleberries, etc.) sweetened with sugar. To children in the second or third years in addition to the fresh milk, potato, vegetable soup, carrots, cabbage, cauliflower, spinach, stewed fruit, green salads, and finally chopped meat.

The foregoing directions are based on the general assumption that greenstuffs will protect against scurvy. Nevertheless, until we know

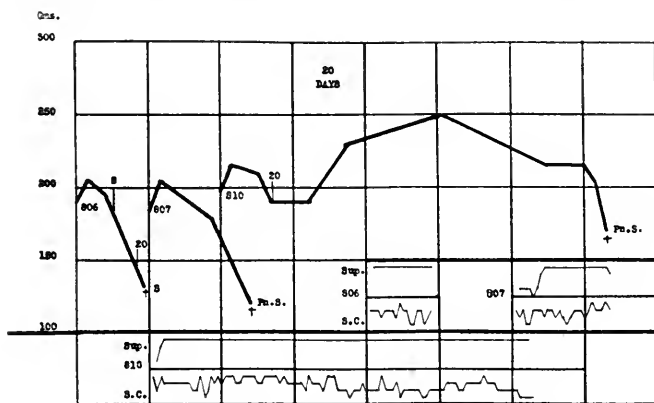


Chart 2.—If fresh bananas are cooked for fifteen minutes at 100 C. their antiscorbutic content is reduced so that 10 gm. daily will not prevent the onset of scurvy. However, 20 gm. so treated prolonged the life of animal 810 for eighty-five days when it died showing evidences of scurvy and pneumonia. 20=20 gm. bananas.

the approximate quantitative antiscorbutic value of each greenstuff, fruits included, we cannot consider these materials interchangeable unless we are prepared to be confronted with failures in the feeding of children and the handling of scurvy, particularly in times of stress. As evidence of the importance of quantity we cite the experience of the British Mission sent to Vienna to study deficiency diseases in children of that city. They report:

Some children in our charge were getting 50 gm. daily of raw apple juice as an antiscorbutic, and to our surprise began to show symptoms of a kind which we had learned to associate with the first onset of scurvy. We had no experimental data as to the antiscorbutic value of raw apple juice; we only knew that it was much inferior to the juice of lemons and many other fruits. We substituted 10 gm. daily of raw neutralized lemon juice with excellent results.²

1. Pfaundler and Schlossmann, 2:194.

2. Brit. M. J. 2:147, 1920.

In previous communications we have detailed the results of quantitative studies of the antiscorbutic potency of cabbage,³ tomatoes,⁴ potatoes,⁵ meat,⁶ and orange juice.⁷ The experiments reported herein deal with apples and bananas. These two fruits are, speaking from an economic standpoint, comparatively cheap, generally available, and consumed by all classes at all seasons of the year.

Holst and Frölich⁸ found that guinea-pigs on a diet of oats, water, and 30 gm. raw bananas daily lived from thirty to fifty-five days. At

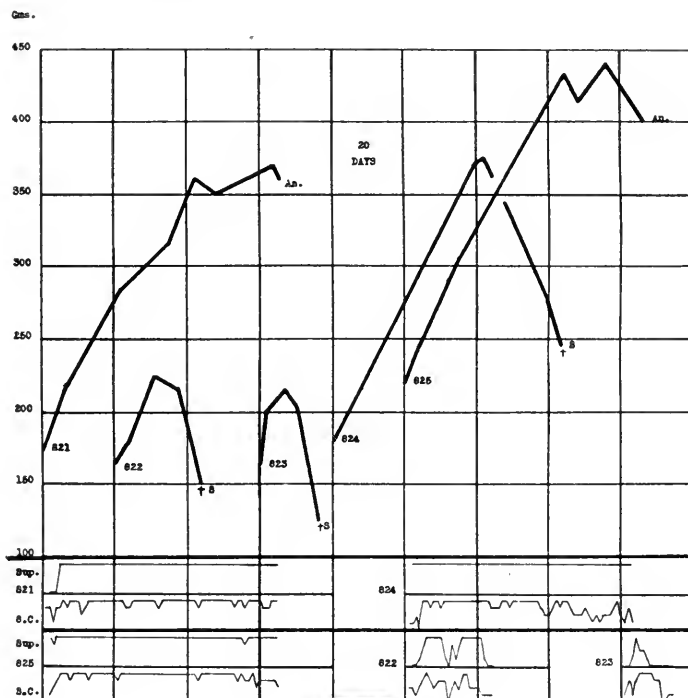


Chart 3.—Ten gm. fresh bananas were cooked at 100 C. for fifteen minutes in 27 c.c. of 0.5 per cent. citric acid. Three out of five animals ate this material satisfactorily. One guinea-pig died at sixty-two days showing signs of scurvy. The other two animals were anesthetized at sixty-five days because it was necessary to terminate the experiments for personal business reasons. These latter animals at necropsy showed signs of scurvy in that a few costo-chondral junctions were enlarged and there were some hemorrhages in the hind legs. The fact that the animals lived longer on the bananas cooked in citric acid than those guinea-pigs fed on bananas cooked in water would indicate that the acidity due to the organic acid had served as a protective agent against the destruction of the antiscorbutic vitamin.

3. Givens, M. H., and Cohen, B.: *J. Biol. Chem.* **36**:127, 1918.
4. Givens, M. H., and McClugage, H. B.: *J. Biol. Chem.* **37**:253, 1919.
5. Givens, M. H., and McClugage, H. B.: *J. Biol. Chem.* **42**:491, 1920.
6. Givens, M. H., and McClugage, H. B.: *Science*, **51**:273, 1920.
7. Givens, M. H., and McClugage, H. B.: *Am. J. Dis. Child.* **18**:30 (July) 1919.
8. Holst, A., and Frölich, T.: *Ztschr. f. Hyg.* **72**:1, 1912.

the necropsy loose molars were observed. Microscopic examination showed a scorbutic alteration in the bone marrow of from one to five ribs in each animal.

The importance of the banana as a foodstuff is not readily grasped when its consumption in this country alone is considered. However, it is given a hitherto unappreciated standing as a food when one realizes that it is the almost exclusive diet—especially during the rainy season

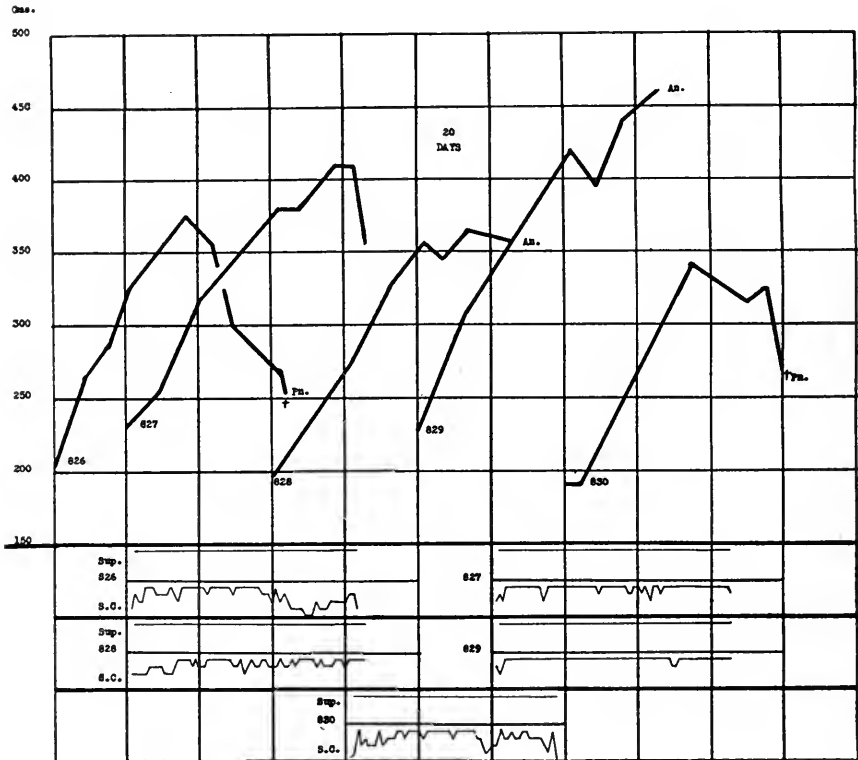


Chart 4.—This group of animals shows that 10 gm. fresh bananas heated in water for fifteen minutes at 60 C. do not contain enough of the antiscorbutic vitamin to prevent the appearance of scurvy at the end of sixty days. The life of the animals has been prolonged for about the same period as in the case of those guinea-pigs on bananas heated at 100 C. in citric acid. Comparing the results shown in this chart with those in Chart 2 it is evident that the heating at 60 C. is not as deleterious as at 100 C. Guinea-pigs 827, 828 and 829 were alive at sixty-five days; the last two were anesthetized and one animal (828) showed slight signs of scurvy.

of about six months' duration—of the peoples of such tropical countries as the East Coast of Africa, the Congo and the Pacific Islands. We know of no reports of scurvy among these peoples and the usage of this food may account for the non-appearance of this disease.

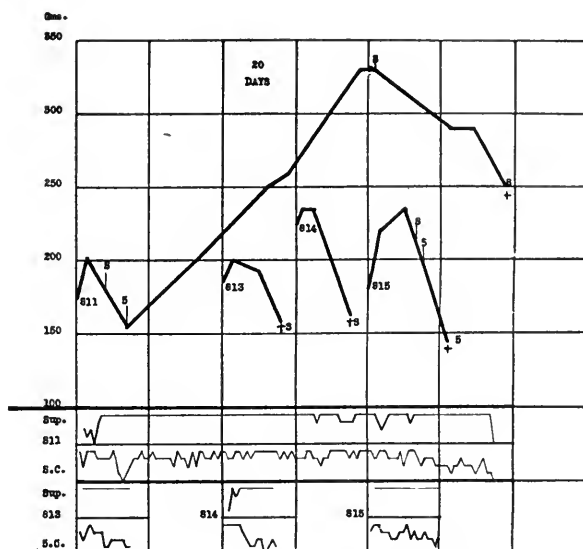


Chart 5.—Bananas were dried at from 55 to 60 C. and fed to the guinea-pigs in this group in doses of 2.5 gm. daily. ^aThis amount of the dried material, equivalent to 10 gm. raw stuff, did not prevent the appearance of scurvy. When guinea-pig 811 had the dosage of dried banana doubled, it apparently recovered from the disease but later developed it again and died therefrom. 5=5 gm.—a daily double dose of bananas.

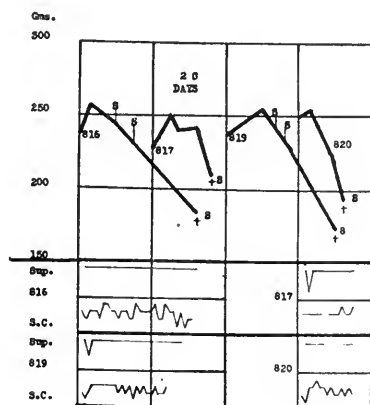


Chart 6.—The results here indicate that dried banana cooked for fifteen minutes at 100 C., even in an amount equivalent to a double dose of the raw food, will afford no protection against scurvy. 5=5 gm.—a daily double dose of bananas.

Sugiura and Benedict⁹ have found that white rats can neither grow nor be maintained on bananas because this foodstuff is deficient in protein and the water soluble B vitamin.

Hess and Unger¹⁰ have used the banana as the source of the anti-scorbutic vitamin in feeding scorbutic children. They state: "In one case banana was given for three weeks without definite improvement, although one half of a ripe banana was fed daily to a baby fifteen months of age." Only slight improvement was noted in another case in which banana was used for almost the same length of time.

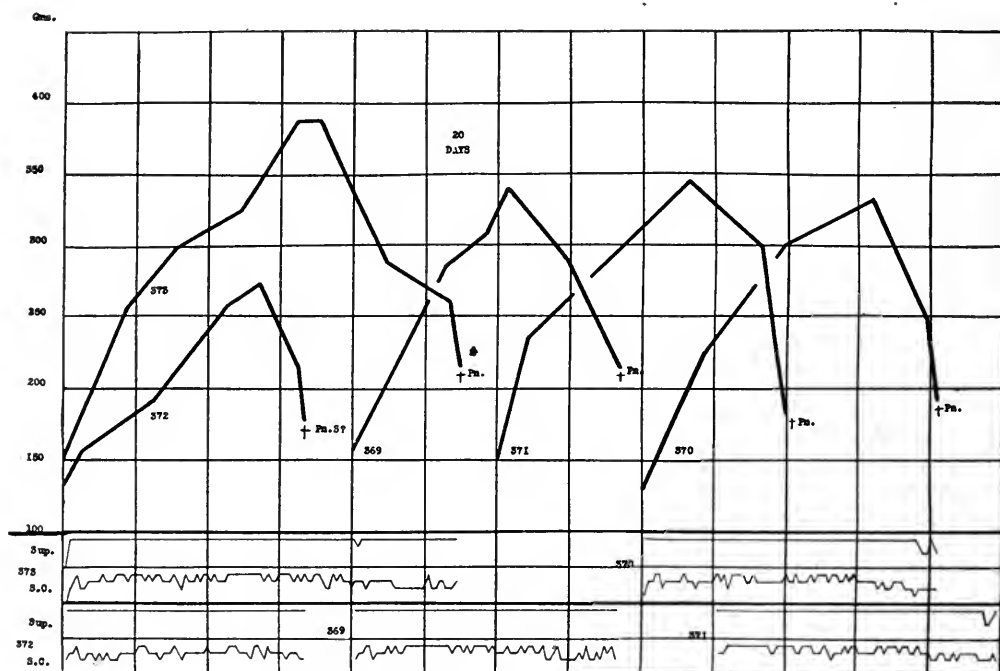


Chart 7.—Ten gm. raw apples were fed daily to each guinea-pig in this group. The animals lived from 67 to 110 days. In one case (372) there was a questionable trace of scurvy. The remaining animals showed no macroscopic evidence of the disease. There was a lung involvement in all animals indicative of pneumonia. In the absence of scorbutic manifestations it seems conclusiv. that 10 gm. raw apples per guinea-pig daily will afford protection against scurvy for a period several times as long as that in which scurvy would have appeared in the absence of the supplement.

Lewis¹¹ found that "bananas in amounts greater than 25 gm. daily as a supplement to a diet of rolled oats prevent the onset of scurvy" in guinea-pigs. When this basal diet was improved by the addition

9. Sugiura, K., and Benedict, S. R.: *J. Biol. Chem.* **36**:171, 1918.

10. Hess, A. F., and Unger, L. J.: *Am. J. Dis. Child.* **17**:221 (March) 1919.

11. Lewis, H. B.: *J. Biol. Chem.* **40**:91, 1919.

of bran, milk, casein and inorganic salts, from 10 to 15 gm. bananas—served to protect the animals against scurvy. The latter result leads this investigator to summarize as follows: "These experiments suggest that a lower content of the antiscorbutic principle may be sufficient to protect against scurvy if the diet is adequate in its content of the other essential dietary constituents." This statement is supported by the experiments which follow.

The apple has been described as "one of the most valued foods that enters into the human dietary both in health and disease."¹²

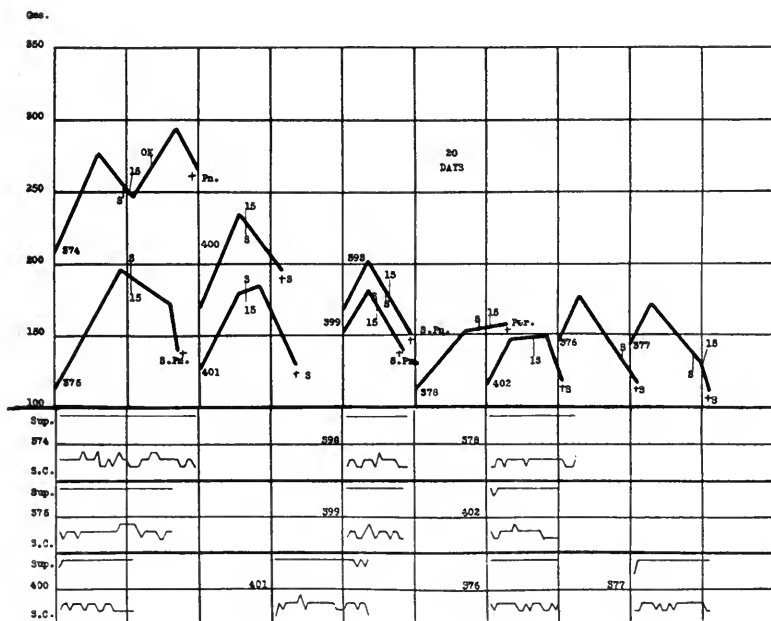


Chart 8.—These experiments show that fresh apples cooked for fifteen minutes at 100 C., even in doses 50 per cent. greater than the raw, afford no protection against scurvy. 15=15 gm. apples—50 per cent. greater than the initial dose.

Osborne and Mendel¹³ have given the experimental proof that this fruit contains the water soluble vitamin B. Holst and Frölich found that guinea-pigs could be maintained for longer than eighty-seven days on rye bread baked with yeast and supplemented with 30 gm. raw apples daily. In two animals, dying on the fifty-first day, there was a slight looseness of molars in one and in the other a few of the ribs showed scorbutic alterations when examined microscopically.

12. Editorial, J. A. M. A. **66**:657 (Sept. 21) 1916.

13. Osborne, T. B., and Mendel, L. B.: J. Biol. Chem. **42**:465, 1920.

Chick¹⁴ and her co-workers state that both fresh and dried apples have a slight antiscorbutic potency.

Carter, Howe, and Mason¹⁵ say: "certain dried fruits and vegetables are also good antiscorbutics—e. g., dried apples, dried tomatoes, strawberries, etc."

EXPERIMENTAL

Sufficient experimental evidence has been produced in the past few years to remove the last vestige of doubt as to the identity of scurvy

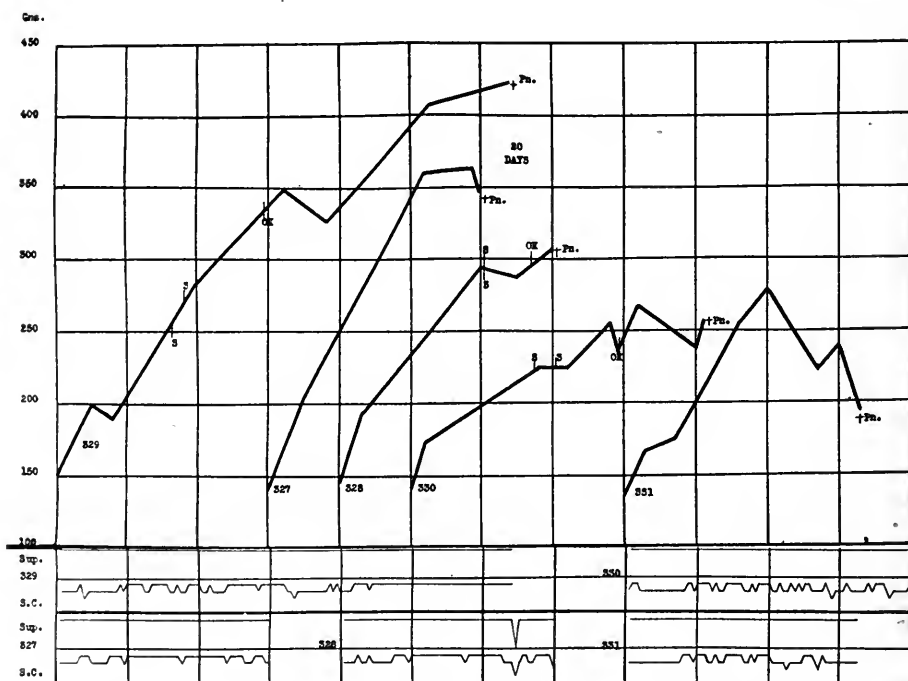


Chart 9.—Apples were dried at from 35 to 40 C. and fed to this group of animals in allotments of 2 gm. daily to each guinea-pig. In the majority of cases scurvy made its appearance but it was arrested and the guinea-pigs apparently cured by a daily dosage of 3 gm. of the dried product. As in the case of the animals on raw apples, pneumonia accounted for the death of all pigs. 3=3 gm. dried apples.

in guinea-pigs and man. The cause of this malnutrition disease and its prevention or cure are the same in both species. Therefore, it is unnecessary to describe the clinical manifestations in guinea-pigs which have been reported in detail in other communications.

14. Chick, H., et al.: Special Report Series, No. 38, Med. Research Com., London, 1919.

15. Carter, H. S.; Howe, P. E., and Mason, H. H.: Nutrition and Clinical Dietetics, Ed. 2, Philadelphia, 1921.

The basal diet to produce scurvy in guinea-pigs—a soy bean flour-milk-yeast-paper pulp-sodium chlorid-calcium lactate combination dried into a cake—is the same that we have used in previous experiments. Likewise, the experimental technic has been the same as formerly reported. All experiments were carried out on healthy young guinea-pigs.*

The Supplemental Foods.—As the source of the antiscorbutic accessory we have used apples and bananas, raw and subjected to various temperature treatments. Details of the supplemental intake of apples and bananas together with the treatment of these foodstuffs are given in Table 1.

TABLE 1.—THE KIND, AMOUNT FED AND TREATMENT OF ANTISCORBUTIC FOODS

Kind	Fed Daily, Gm.	Dried at Degrees C.	Duration of Drying Hours	Cooked 15 Minutes at Degrees C.	Per Cent. of Original Weight
Apples:					
Raw.....	10
Raw.....	10	100
Dried.....	2	35-40	5-6	...	18-19
Dried.....	2	35-40	5-6	100	18-19
Dried.....	2	55-60	4-4.5	...	16-17
Dried.....	2	55-60	4-4.5	100	16-17
Dried peelings.....	2	35-40	5.5-6.5	...	23-26
Dried peelings.....	2	55-60	4.5-5	...	22
Bananas:					
Raw.....	10
Raw.....	10	100
Raw.....	10	100*
Raw.....	10	60
Dried.....	2.5	55-60	6-7	...	26-27
Dried.....	2.5	55-60	6-7	100	26-27

* Cooked in 0.5 per cent. citric acid.

The raw apples and bananas were such as the market afforded from December to June. These foods were considered ripe in the ordinary usage of the term, which of course means in the case of bananas only, that the skin was a deep golden color and therefore not completely ripe. The foods were dehydrated by means of hot air in a manner previously described.⁴ The desiccated foods were used within two and a half months of drying. Approximately the same amount of food in terms of original raw material was fed in all experiments. In cooking the materials, water, or 0.5 per cent. citric acid, sufficient to cover the foods (about 27 c.c.) was used and the cooking medium was fed with the food. This procedure avoided any loss of vitamins by extraction. All material to be cooked was sliced very thin, poured into the medium (boiling or at 60 C.) and as soon as the desired temperature was regained, which was within two or three minutes, it was maintained for fifteen minutes. Of course, cooking at 100 C., for fifteen minutes, ruptured all starch granules and stopped enzyme action. It was found that the same thing was accomplished in the case of bananas heated to 60 C.

RESULTS

As we have shown previously, a guinea-pig on the basal soy cake diet alone will die of scurvy in from fifteen to twenty-five days. For the sake of comparison we will set the upper limit of life at thirty days in the absence from the diet of the antiscorbutic accessory. If the animal lives for sixty days, it is considered that a fair degree of protection has been afforded. When the animal lives for ninety days or longer there seems to be no doubt that the antiscorbutic factor is present in sufficient amount to protect completely against scurvy.

The conclusions given in Table 2 are based on the above standards. Details of each animal are given in the notes at the foot of the curves.

TABLE 2.—RESULTS WITH DIFFERENT PRODUCTS

Kind of Food	Daily Intake, Gm.	Dried at Degrees C.	Cooked 15 Min. at Degrees C.	Protection Afforded
Apples:				
Raw.....	10	Complete protection
Raw.....	10	100	No protection
Dried.....	2	35-40	...	No protection with 2 gm., some with 3 gm.
Dried.....	2	35-40	100	No protection even with 3 gm.
Dried.....	2	55-60	...	Some protection
Dried.....	2	55-60	100	No protection even with 3 gm.
Dried peelings...	2	35-40	...	Apparently complete protection
Dried peelings...	2	55-60	...	Apparently complete protection
Bananas:				
Raw.....	10	Complete protection
Raw.....	10	100	No protection with 10 gm., some with 20 gm.
Raw.....	10	100*	Some protection
Raw.....	10	60	Some protection
Dried.....	2.5	No protection on 2.5 gm., some with 5 gm.
Dried.....	2.5	100	No protection even with 5 gm.

* Cooked in 27 c.c. 0.5 per cent. citric acid.

DISCUSSION

These experiments demonstrate that the raw apple and the raw banana are antiscorbutic agents. However, if either of these foods is subjected to any considerable temperature treatment, such as ordinarily employed in preservation by desiccation or canning, the amount of antiscorbutic vitamin in the original raw material is markedly reduced. This finding is in contrast to the statement of Chick and associates and that of Carter, Howe and Mason that the dried apple is an antiscorbutic agent. Of course, the banana is ordinarily and the apple generally eaten raw. Nevertheless, both these foods are served cooked, and it is hardly conceivable that one would feed either to a very small infant without thorough cooking. When such heating is employed cognizance must be taken of the fact that the antiscorbutic property of these foods has been markedly decreased if not entirely destroyed. The use of dried apples in cooked form is almost universal. In the light of these experiments such heat treated preparations must be considered as unreliable sources of the antiscorbutic vitamin.

In an investigation of the antiscorbutic property of raw and variously heat treated potatoes we stated that "the influence of heat on the antiscorbutic vitamin appears to be related not only to the degree of temperature but to the duration of the treatment, the reaction, the enzymes present and the manner of heating." The experiments on apples and bananas offer further support for this statement. Dehydrating apples at from 35 to 40 C. is more destructive of the antiscorbutic vitamin than desiccating at from 55 to 60 C. This undoubtedly is due, in part, to the longer period of heating necessary for drying at the lower temperature. Delf¹⁶ has noted the same fact, as she states "the least loss of antiscorbutic properties will be obtained by cooking green vegetables for a short time at a higher temperature rather than for a longer time at a lower temperature."

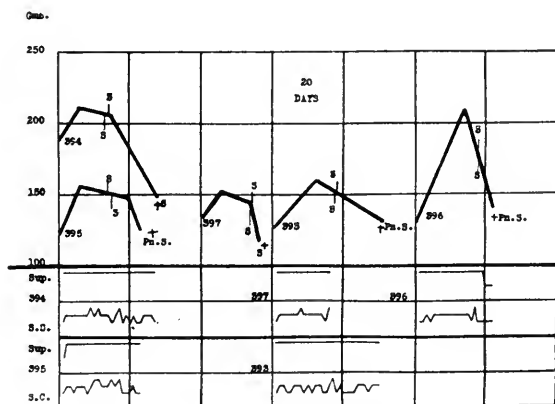


Chart 10.—This chart shows that apples dried at from 35 to 40 C. and cooked for fifteen minutes at 100 C. afford no protection against scurvy. The protective action shown by 3 gm. of this material (Chart 9) is destroyed by heating for fifteen minutes at 100 C. 3=3 gm. dried apples.

Bananas cooked for fifteen minutes at 100 C. afforded the animals no protection. When the fruit was cooked for the same period at the same temperature in the presence of dilute citric acid there was evidently not as much destruction of the antiscorbutic vitamin. In the case of potatoes⁵ it was found that citric acid was not destructive and may have acted as a protective agent. There was more destruction of the antiscorbutic vitamin in bananas cooked for fifteen minutes at 100 C. than for the same period at 60 C. This result is in accord with Delf's work on cabbage.

All the dried products were used within two and a half months of dehydration. This period of storage is too short to consider its possible destructive influence. However as the dried products were

16. Delf, E. M.: *Biochem. J.* **12**:416, 1918.

almost useless as antiscorbutic agents and therefore of no practical value, it is unnecessary to take into consideration this factor.

It is exceedingly important that the exact antiscorbutic value of the various foods be known. The actual proof of this need has been referred to in citing the experience of the British in feeding the children of Vienna in 1920. Feeding experiments on animals are relatives and, of course, cannot be strictly quantitative until the vitamins are isolated in a more or less pure condition. However, such data afford means of judging the value of foods and permitting substitution

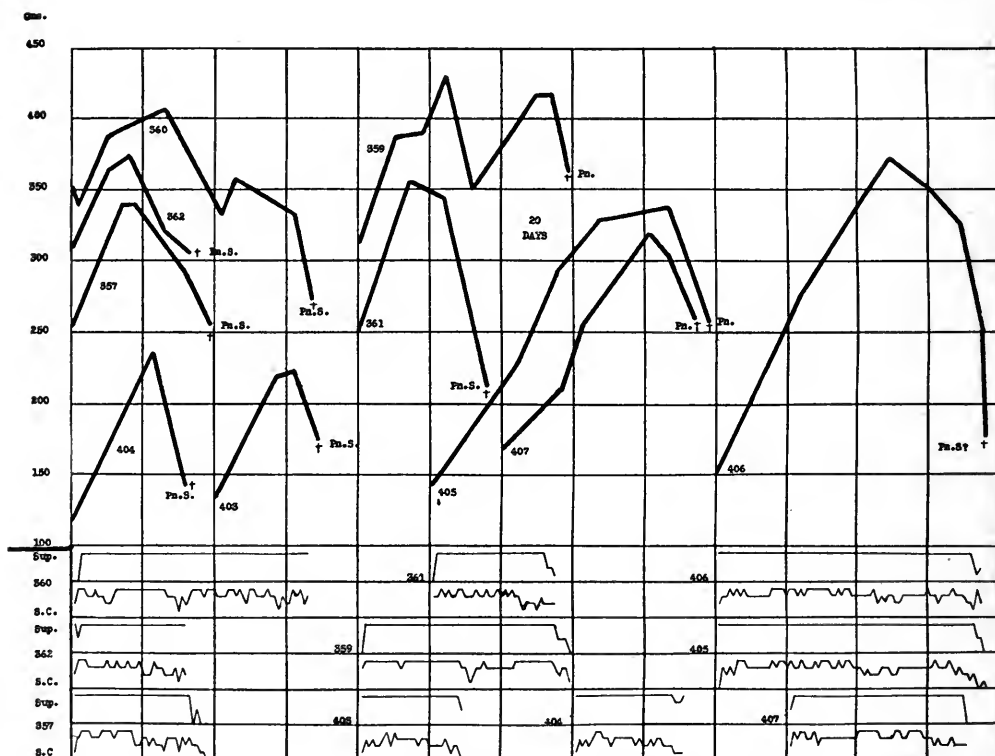


Chart 11.—To each animal in this group there were fed daily 2 gm. apples dried at from 55 to 60 C. No better protection seems to be afforded by apples dried at this temperature than by those dried at from 35 to 40 C. That there has been some protection, however, is evident from the length of life of the guinea-pigs.

with some degree of accuracy. For example if 1.5 c.c. of lemon juice and 10 gm. raw apples are the minimum amounts necessary to protect guinea-pigs against scurvy, then for a child doing satisfactorily on 10 gm. lemon juice, the British ought to have been able to substitute 67 gm. raw apple. Whether or not the results would have been the same had they fed raw scraped apple equivalent to the amount of apple

necessary to yield 50 gm. juice is a question. Not only the antiscorbutic content of the apple itself but also whether most of the antiscorbutic vitamin is obtained by expressing the juice, enters into consideration. In other words, is it a product within the cells not easily extracted or is it excreted by the cells and, therefore, more or less dependent on the amount of fluid in the fruit.

An interesting question for future solution is whether or not the maximum antiscorbutic content of a food is dependent on its maturity. In the case of the fruits under consideration is the amount of antiscorbutic vitamin greater in a fully ripe banana and apple, or not?

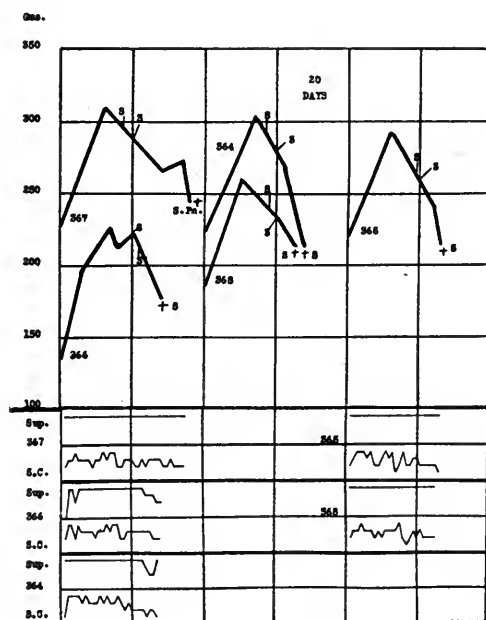


Chart 12.—Apples were dried at from 55 to 60 C., cooked for fifteen minutes at 100 C. and fed in doses of 2 gm. (of dried material) daily. No protection was afforded the animals, even when the dose was increased to 3 gm. daily. 3=3 gm. dried apples.

If such a relationship exists then the intake of the antiscorbutic accessory will never be known exactly because we eat fruit in all stages of ripening. If so-called ripening is merely a transformation of starch into sugar, then it is unlikely that the antiscorbutic content is affected. However, if cellular reproduction continues, then it is a fair assumption that there is an alteration in the amount of antiscorbutic vitamin present. That the dried apple peelings were a better antiscorbutic agent than the dried apples would seem to indicate that the vitamin is associated with cells inasmuch as there are more cells in the peeling than in the

body of the apple. Support is lent to the idea by the work of Chick and Hume¹⁷ who showed that unsprouted beans did not contain the anti-scorbutic principle, but if sprouting occurred, and, therefore, cellular reproduction, there was a production of this important accessory. In the case of apple peelings we are not unmindful of the possibility that the cellulose covering of the apple may have acted as a protective agent against the destructive influence of the heat of dehydration.

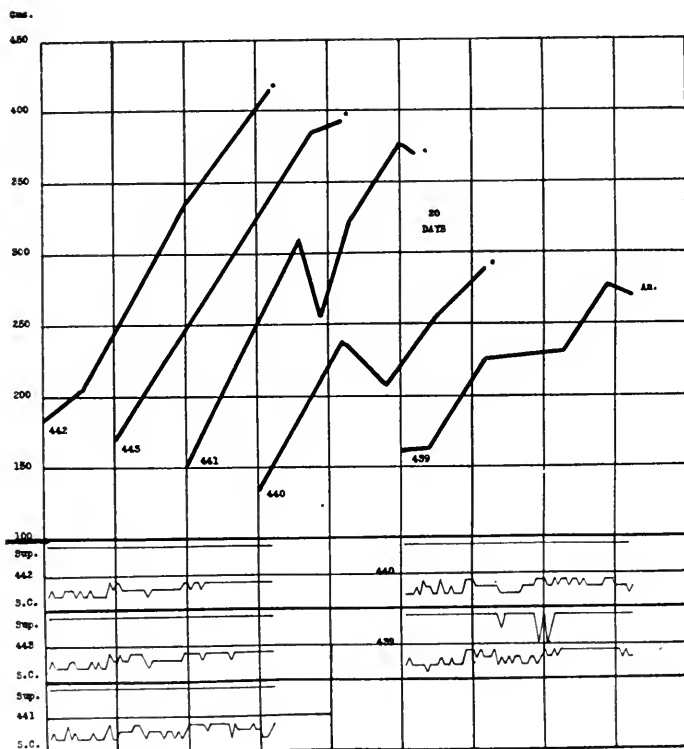


Chart 13.—Peelings from the apples were dried at from 35 to 40 C. and from 55 to 60 C. The animals in this group received daily 2 gm. dried peelings per guinea-pig; for the first twenty days those dried at from 35 to 40 C. and thereafter those dried at from 55 to 60 C. The animals were carried over sixty days on this regime without clinical signs of scurvy. Animal 439 anesthetized at sixty-five days showed no signs of scurvy at necropsy. The results with the peelings are in striking contrast to those with the apples.

From a practical standpoint it is doubtful whether dried bananas will ever be used in this country. Such cannot be said for the cooked fruit as we find its use advocated for the young¹⁸ and for nephritics.¹⁹

17. Chick, H., and Hume, M.: *Tr. Soc. Trop. Med. & Hyg.* **10**:141, 1917.

18. Pease, M. C., and Rose, A. R.: *Am. J. Dis. Child.* **14**:379 (Oct.) 1917.

19. Myers, V. C., and Rose, A. R.: *J. A. M. A.* **68**:1022 (April 7) 1917.

Accordingly, cognizance must be taken of the fact that the cooked material has had its antiscorbutic content reduced. As regards apples, all of the experiments are of practical value. Where fresh apples cooked and dried apples cooked are consumed it must be remembered that the amount of antiscorbutic vitamin in the original raw material is no longer available because some destruction has been wrought by the heat of preparation.

INDICES OF THE STATE OF NUTRITION IN CHILDREN *

H. GRAY M.D., AND G. H. EDMANDS

BOSTON

THE PROBLEM: *What is the normal state of nutrition for this child?*

The doctor's answer too often has depended on the shifting sands of subjective impressions. In the search for a solid objective standard, we have hunted through a quantity of books and articles on diseases of nutrition, metabolism, obesity and the like, many of them by writers of established reputation, but have been surprised and disappointed at the complete omission of a standard of nutrition in many of these monographs, and among the rest at the un-uniform "standards." This lack of uniformity not only catches the eye during casual perusal but on comparison becomes astounding, as we have pointed out in previous papers on body weight.¹ We have also reported the case of a healthy child, aged 4 years, whose weight agreed exactly with one standard but differed from another standard by 31 per cent.

Averages of weights and heights are the time-honored basis of the different standards. But as objections have been made to the use of averages, a few remarks may be in place. It is admitted that many normal persons differ considerably from the averages; for example, that the normal weight (for a given age, standing height, sitting height, or other measurement) is not a line but a zone. At the same time, we feel with Schwiening² and others that averages are at present the best available criteria; that is, that they are neither unduly high, owing to a peculiar number of heavy children among those observed, nor unduly low, owing to a peculiar number of thin children. This, as a general rule, seems true, although we have tried in this paper to give greater precision by utilizing boys of so-called upper strata of society, and, further, excluding those boys who seemed subnormal. In other

* Received for publication, Oct. 26, 1921.

1. Gray, H., and Gray, K. M.: Boston M. & S. J. **177**:894 (Dec. 27) 1917.

Gray, H., and Mayall, J. F.: Arch. Int. Med. **26**:133 (Aug.) 1920.

Gray, H., and Allen, F. B.: Boston M. & S. J. **184**:334 (March 31) 1921.

Gray H., and Root, H. F.: Boston M. & S. J. **184**:439 (April 28) 1921.

Gray, H., and Root, H. F.: Boston M. & S. J. **185**:28 (July 7) 1921.

Gray, H.: M. Clinics N. America, **4**:1899 (May) 1921.

Gray H., and Jacomb, W. J.: Am. J. Dis. Child. **22**:259 (Sept.) 1921.

Gray, H.: Am. J. Dis. Child. **22**:272 (Sept.) 1921.

Gray, H., and Walker, A. M.: Am. J. Physical Anthropology, **4**:231 (July-Sept.) 1921.

2. Schwiening, H.: Deutsch. med. Wchnschr. **40**:498, 556 (March 5 and 12) 1914.

words, we think that our averages are adequate for the present purpose, which is to ascertain by what method one may estimate the nutrition of a child with the least error.

Once some standard has been proven superior, it will certainly be desirable to determine the "distribution"; that is, the number of children above and below the average, and the extent to which the extreme normals are found to differ from the average.

This distribution has already been reported by various observers for the weights of persons of given statures, but this ratio $W:H$ is being superseded by the relationship of weight to other anthropometric measurements (stem-length, chest-girth), as among others we have been interested in reporting.¹

Similarly, from our viewpoint, it will be desirable to determine the average and distribution (1) for each age of stem-lengths and chest-girths; (2) for each stem-length of weights and of chest girths, and (3) for each chest-girth of weights.

SYNOPSIS OF STUDIES ON INDICES OF NUTRITION

Other methods have previously been surveyed by us in several places, hence attention will be confined to an attempt to summarize more recent methods. Most of these deal primarily with weight in relation to age or to some measurement, while a few deal with measurements, but not weights, in relation to age.

Perhaps the simplest way of guessing the state of nutrition is by the Dunfermline scale, by which a child is eyed and ticketed I, II, III or IV. Such an estimation must be granted a certain merit when made by an experienced observer, but crudeness of this kind is neither satisfactory in theory, nor in practice has it been justified by those who have reported comparisons of it with more exact systems.

Oppenheimer³ judged the state of nutrition only after making in infants the following elaborate notations: age, weight, height (H), and the circumferences of head, chest (C), belly, right upper arm, left forearm, right thigh, and left calf. In order to simplify these to a working basis, he experimented with the formula $C \times$ upper-arm-girth divided by H . This "measure of nutrition" he found for well nourished infants generally from 8 to 9, but with such marked exceptions that he felt obliged to try another formula. This he called the "Nutrition quotient": $100 \times$ upper-arm-girth divided by C , and he found it to be from 30 to 31, but again with extraordinary extremes. However, he ventured his judgment after examining these two indices. This seems both too complex and too subjective.

3. Oppenheimer, K.: *Deutsch. med. Wchnschr.* **35**:1835 (Oct. 21) 1909.

Oeder ⁴ has studied nutritional indices in adults, in a series of papers from 1908 to 1920.⁴ He lays the greatest emphasis on the relation which he believes to exist between the body-weight and what he calls the proportional-length. This proportional length is twice the distance from the top of the skull to the middle of the pubic bone. This contention is not supported by evidence which we recently published.¹

Oeder also reported studies of the muscular development by measuring the upper arm-girth with the biceps contracted and relaxed, then analyzing the difference between the two measurements, but found this no good.

More worthy of consideration are the signs of the normal state of nutrition which Oeder has laid down: (1) invisibility of the intercostal spaces near the sternum; (2) invisibility of the intertendon spaces on the backs of the hands; (3) equal level of abdomen and chest when supine; (4) abdominal fat layer of from 2 to 3 cm. at the base of a fold picked up parallel to the body axis and just to the right of the navel (Indexstelle; Vergleichsstelle), and measured to the nearest quarter centimeter with ordinary obstetric or special calipers, one tip of which is placed about 1 cm. to the right of the navel. For this "Fettpolstermessung" he found nearly the same figures from 2 to 3 cm. (average for men 2.5 cm., for women 2.7 cm.) in normals of both sexes and all adult ages (he studied men of 24 years and over, women 21 and over). While granting that the distribution of the fatty layer varies slightly in the sexes and at different ages, he found the variation so small that "the normal state of nutrition generally can be defined fairly accurately for any subject by the same measurement, the 'Index-fettpolsterdicke' alone." The nutrition he would often consider normal, even in the absence of one or the other of these signs, most frequently the second.

Of these signs the most objective is clearly the fat-layer. With regard to it Peiser ⁵ said:

The older doctors have always, in order to orient themselves on the state of nutrition of a child, picked up and felt a fold of skin. They chose, as a rule, the skin of the cheek. The children, to be sure, have generally regarded this as a joke. . . . Czerny has constantly pointed out that . . . the consideration of the lower half of the body is more important than the upper. . . . The first to carry out systematic measurements of the fat-layer was Oeder in adults.

4. Oeder, G.: *Deutsch. med. Wchnschr.* **35**:1079 (June 11) 1908; *Ztschr. f. Versicherungsmedizin*, 1909 (not seen); *Med. Klin.* **4**:461 (March 28) 1909; *Id.* **5**:1225 (Aug. 15) 1909; *Id.* **6**:657 (April 24) 1910; *Fortschr. d. Med.* **29**:961 (Oct. 12) 1911; *Deutsch. med. Wchnschr.* **40**:917 (April 30) 1914; *Berl. klin. Wchnschr.* **52**:433 (April 26) 466 (May 10) 1915; *Berl. klin. Wchnschr.* **52**:1086 (Oct. 18) 1915; *Deutsch. med. Wchnschr.* **42**:1073 (Aug. 31) 1916; *Ztschr. f. exper. Path.* **21**:263 (Aug. 26) 1920; *Münch. med. Wchnschr.* **67**:1368 (Nov. 19) 1920.

5. Peiser, J.: *Jahrb. f. Kinderh.* **95**:195, 1921.

With careful measurements at the same place Oeder seldom found a greater difference than 0.25 cm. This, compared with his average 2.75 cm. for 607 normal adults (his 936 thin people averaged 1.1 cm. and his 377 fat people 4.4 cm.), we notice to constitute an error of about 9 per cent. True, he states this as his outside error, but he admits that the technic requires the greatest care and considerable practice. One wonders how large the error would be in the hands of the busy practitioner or school examiner.

In children, Oeder's abdominal fat-layer has received attention from Neumann⁶ and Batkin.⁷ Their results support the hope that the method may be proved useful, but afford only partial proof in that their results, as noted by Peiser, fail to coincide. For instance, we see that Neumann found for boys from 4 to 13 years an average abdominal fat-layer of 5 mm., whereas Batkin found for boys from 5 to 10 years an average of 13 mm., or more than twice as great.

From these figures it is apparent that children have an abdominal fat layer only one quarter or one half that of adults.

Rohrer⁸ proposed his index of the Körperfülle as a measure of the state of nutrition. This index $100 W/H^3$ has been regarded by Oeder as theoretically no better than the nearly identical and often rejected formulae of Buffon⁹ (W/H^3) and of Livi¹⁰ $100 \sqrt[3]{\frac{W}{H^2}}$. In practice, too, apart from its wide use as a standard for the selection of undernourished German children to receive the food so generously given by the Quakers, Rohrer's index seems to have been denounced all the way from dubious to "very bad," by Matusiewicz,¹¹ Bachauer and Lampart,¹² Davenport,¹³ Hamburger and Jellenigg,¹⁴ Schlesinger,¹⁵ Wagner,¹⁶ Bokofzer,¹⁷ Pfaundler,¹⁸ Kaup¹⁹ and Huth²⁰. Less adverse are Bardeen²¹ and Berliner.²²

6. Neumann, H.: *Jahrb. f. Kinderh.* **75**:481, 1912.

7. Batkin, S.: *Jahrb. f. Kinderh.* **82**:103, 1915.

8. Rohrer, F.: *Corr.-Bl. d. Deutsch. Gesell. f. Anthropologie* **39**:5 (Jan.-Feb.) 1908; *Münch. med. Wchnschr.* **68**:580 (May 13) 1921; *Münch. med. Wchnschr.* **68**:850 (July 8) 1921.

9. Buffon, G. L. L. de: *Oeuvres complètes*, Bruxelles, 1833.

10. Livi, R.: *Arch. ital. de Biol.* **32**:299, 1899, rev. in Hoffman: *Schmidt's Jahrbücher* **266**:221, 1900.

11. Matusiewicz: *Inaug.-Diss.*, München, 1914.

12. Bachauer and Lampart: *Münch. med. Wchnschr.*, **67**:1296 (Nov. 5) 1920.

13. Davenport, C. B.: *Am. J. Physical Anthropology*, **3**:467 (Oct.-Dec.) 1920.

14. Hamburger, F., and Jellenigg, K.: *Wien. klin. Wchnschr.* **33**:1131 (Dec. 23) 1920.

15. Schlesinger, E.: *Münch. med. Wchnschr.* **67**:1523 (Dec. 31) 1920.

16. Wagner, R.: *Ztschr. f. Kinderh.* **28**:38 (Feb. 14) 1921.

17. Bokofzer: *Münch. med. Wchnschr.* **47**:593 (May 26) 1921.

18. Pfaundler, M.: *Münch. med. Wchnschr.* **68**:974 (Aug. 5) 1921.

19. Kaup, J.: *Münch. med. Wchnschr.* **68**:976 (Aug. 5) 1921.

20. Huth, A.: *Ztschr. f. Kinderh.* **30**:39 (Aug. 19) 1921.

21. Bardeen, C. R.: *Carnegie Pub. No. 272*, Washington, D. C., 1920, p. 483.

22. Berliner, M.: *Berl. klin. Wchnschr.* **58**:58 (Jan. 17) 1921.

Without referring to these unfriendly comments, Rohrer stated that possibly one should use three indices:

I 1=Height,

I 2=Some body width, such as the shoulder or pelvic breadth (intercrystal diameter),

I 3=Some body depth measurement, such as the sagittal thoracic or the average of this and the sagittal pelvic diameter.

Similar diameters have been suggested before, without result, and indeed complexity would seem to bar this method.

Sperk²³ measured (1) as an index of musculature: the girths of the neck, chest and upper arm; (2) as an index of fat: the circumferentia minima abdominalis of Lenhoff, because he found this to show individual differences better than Oeder's method; and finally, (3) as a measure of the bones: he used the girth of the lower end of the fore arm. The utility of these measurements remains to be proved.

Huth²⁰ measured thirty-one pupils of an average age of about 11 years: H, W, C, shoulder breadth, upper arm girth, waist girth, and thigh. His utilization of these measurements does not seem helpful at present. His statistical analysis, however, deserves attention, in view of the recent papers by Pearl,²⁴ Harris and Benedict,²⁵ Dreyer and Walker,²⁶ Kilgore²⁷ and Feldman,²⁸ emphasizing the vast latent possibilities of medical progress by statistics made by the improved biometric methods. Owing, however, to the present unfamiliarity of medical men with biometric complexities, we venture to think our method for testing standards as given below is simpler and we hope adequate.

Huth tried to solve the question "Are the body measurements a function of the state of nutrition or not?" by the use of the coefficient of correlation (r), which he calculated for seven different standards.

His conclusion was that since in all these r was negative (from -0.02 to -0.15), there existed no correlation between state of nutrition and body measurement indices, and, therefore, no functional connection. With this inference we agree, but think he is outrunning his evidence when he goes on to say: "hence it is not permissible to try to establish the state of nutrition with the help of body measurement indices. . . . We ought to get a correlation of at least $+0.6$ in order to regard an index as half way reliable."

23. Sperrk, B.: Wien. klin. Wchnschr. **34**:210 (May 5) 1921; Abstr. Boston M. & S. J. **185**:66 (July 14) 1921.

24. Pearl, R.: Arch. Int. Med. **24**:398 (Oct.) 1919; Johns Hopkins Hosp. Bull. **32**:184 (June) 1921.

25. Harris, J. A., and Benedict, F. G.: Carnegie Publication No. 279, Washington, D. C., 1919, pp. 1, 9 and ff.

26. Dreyer, G., and Walker, E. W. A.: Contributions to Medical and Biological Research (Osler), N. Y. **1**:40, 1919.

27. Kilgore, E. S.: J. A. M. A. **75**:86 (July 10) 1920.

28. Feldman, W. M.: Brit. J. Child. Dis. **17**:171 (Oct.-Dec.) 1920.

OTHER STANDARDS SELECTED FOR STUDY HERE

Besides the methods just reviewed, there are three others which have appealed to us as the most promising in the literature: Von Pirquet's,²⁹ Dreyer and Hanson's,³⁰ and the Ideal size and weight tables recently reported by us.¹

Methods for predicting the normal weight for a given person from one or more of his physical measurements have been proposed from time to time; but have surprisingly seldom (apart from Huth's valuable contribution) been tested simultaneously on the same series of healthy children. Even a brief test will reveal astoundingly diverse weights for one and the same subject, according to the formula applied. The conclusion seemed fair therefore that more study was necessary to determine which of these competing "standards" was most worthy of the name, and also to indicate if possible which physical measurements are in future most worth recording.

The results so far, though tedious, are encouraging. Dreyer and Hanson's new book of tables leads the field, judging by evidence which we have recently assembled regarding adult men and a few boys of preschool and school age.¹ Indeed, one is almost swayed by enthusiasm when one has been able to show a mother intelligent enough to be worried because her child seemed 30 per cent. too fat by such an approved standard as Holt's,³¹ that according to Dreyer and Hanson's prediction the child weighed within 1 per cent. of what he should.

It may be convenient to present here the more practical details of these three methods, while referring any interested reader to our fuller critique elsewhere.¹

The Ideal tables just mentioned were arrived at in the following manner. In routine examinations of well-to-do and healthy boys in country day and boarding schools, we had been impressed by the unfitness of the usual pediatric tables for height and chest-girth in relation to age, and for weight in relation to height. This was easily explained by the fact that the usual tables had been constructed from observations on public school children, and that too without exclusion of those children who were clinically below par. New and different standards, constructed from observations on the cultured class of boys, seemed to us indispensable, and we, therefore, published the averages of our observations on 380 such boys, aged from 6 to 20 years. We

29. Pirquet, C.: *Ztschr. f. Kinderh.* **6**:256, 1913; **14**:211, 1916; also reprinted in his book "System der Ernährung," Berlin, 1919, **2**:284; *Ztschr. f. Kinderh.* **18**:220, 1918; *Osterreichischen Rundschau*, **63**:10, 1920 reprint.

30. Dreyer, G., and Hanson, G. F.: *The Assessment of Physical Fitness*, London, 1920; reprinted by Hoeber, N. Y., 1921.

31. Holt, L. E.: *Diseases of Infancy and Childhood*, New York, Ed. 8, 1919

hoped, of course, that this way of attack would be followed by others who could command larger material, accumulate vaster data, and on that basis construct less tentative tables.

Our Ideal Tables showed the average height for age, chest-girth for age, weight for age, and finally what had received scant notice but seemed to us useful, weight for chest-girth. This last standard, chest-girth, we wish to insist on, as very probably affording the most valuable of all so far suggested, provided a single measurement be desired. For an example, see Table 1, last column, fourth row up, 2 per cent.

Pirquet judged weight in relation to sitting height by means of his index which he first called the Gilidusi. This he then amended to the Gelidusi, or cube root of ten times the weight in grams divided by the sitting height in centimeters:

$$\frac{\sqrt[3]{10 \times W}}{Si} = 100$$

Still later he proposed a new name for the same index: Pelidisi, compounded of the initials of Latin (perhaps for foreign consumption) instead of German words. His ideas have been discussed by Bernstein,³² Von Gröer,³³ Schick³⁴ and Faber.³⁵ As the latter has pointed out, there are "certain minor inaccuracies and disagreements" in Pirquet's writings. The most important of these inaccuracies seems to be in his formula:³⁶ $100 (10 \times W \text{ in g.})^{2/3} \div Si = 100$.

If, now, this two-thirds power be considered a misprint for one-third, the formula will read: $100 \sqrt[3]{10 \times W \text{ in g.}} \div Si = 100$, in which case the Pelidisi will come out approximately a hundred instead of yielding a decimal (as is given by the first sample printed above, according to Pirquet's 1916 article, p. 216). This proposed correction represents correctly, we believe, Pirquet's theory. His formula has found so much favor in feeding the children of Austria that it must be tested.

It would seem that the fundamental idea underlying the Pelidisi index might be stated in a style more like the weight prediction formulae used by others. For example, instead of his conclusions that Index Pelidisi $\sqrt[3]{10 \times \text{weight} \div \text{sitting height}}$ in muscular adults and plump infants averages 100, and in grown children 94, it seems more practical to say that for (1) adults: $W \text{ (in g.)} = Si^3 \text{ (in cm.)} \div 10$, and for (2) growing children: $W \text{ (in g.)} = (0.94 Si)^3 \div 10$.

32. Bernstein, F.: *Ztschr. f. Kinderh.* **16**:78, 1917.

33. Von Gröer, F.: *Ztschr. f. Kinderh.* **18**:287, 1918 (Sonderheft).

34. Schick, B.: *Das Pirquetsche System der Ernährung*, Berlin, Ed. 2, 1919, p. 27.

35. Faber, H. K.: *Am. J. Dis. Child.* **19**:478 (June) 1920; See also his chart showing Sitting Height—Weight Nutritional Index of Von Pirquet (Pelidisi), reproduced and distributed by San Francisco Tuberculosis Assn., 1921.

36. Pirquet: *System der Ernährung*, **2**:287, 1919.

Hamburger and Jellenigg said that a cursory valuation of their cases indicated that the Pelidisi method yields an error of hardly less than 40 per cent., and we have reported¹ two cases in boys of 4 and 3 years, respectively, in which the error of the Pelidisi was 31 and 22 per cent., respectively. The error in our present series of 114 school boys was 21.5 per cent.

Dreyer realized, as had Bornhardt³⁷ but practically nobody else before him, that in predicting weight body-length alone was inadequate. Like the Russian military surgeon, he made simultaneous use of the chest measurement, but substituted stem length for stature, and constructed his formula in an entirely different fashion.

Dreyer and Hanson then used the stem length of Walker,³⁸ a measurement generally about 3 per cent. smaller than the sitting height but having the advantage that it can be determined with more accuracy and constancy.

TECHNIC

The length (λ) is measured by seating the subject on the floor or on a low table (not a chair) with the back against the wall. Care is taken to see that the sacrum is in contact with the wall, and the legs somewhat drawn up so that the individual sits fairly on his ischial tuberosities. Under these conditions the height of the top of the head gives a true measurement of the length of the body, and one which is constant and incapable of variation by the subject. If a chair or other form of seat be employed in taking this measurement the individual can by "sitting low" or "sitting high" produce at will a variation of as much as 3 per cent. or more. But, since a subject conscious that he is being measured for height tends naturally to produce a full measurement, it will be found that he intentionally "sits up," straightening the spine, tilting the pelvis forward, and rests on the contracted muscles of the thighs and buttocks instead of on his ischial tuberosities. The apparent length—"sitting height," as it has been termed—is thus increased by between 2 and 3 per cent. above the measurement taken in the manner already described. Accordingly measurements taken on a seat require to be corrected down appropriately before they can be treated as comparable with the measurement of body-length in infants or animals. (Walker³⁸).

The subject places the backs of the fingers on the platform on which he sits, and, with the fingers pointing backward and the knees flexed, lifts the lower portion of the body gently backward until the lowest bony portion of the os sacrum is in contact with the front of the measuring standard. The back is then straightened until the back of the head comes into contact with the standard. It will be found that different persons require to bend the knees in different degrees in order to achieve this position. The head should be tilted neither up nor down and the eyes should look straight forward (Dreyer).

Simultaneously with their table of weights for stem-length, Dreyer and Hanson use a table of weights for chest-girth, and average together the two values obtained in order to make their prediction of the normal weight for the person measured.

37. Bornhardt, A.: *St. Petersburg. med. Wchnschr.* **3**:108 (March 22) 196 (April 3) (May 24) (June 5) 1886; *id.* **5**:413 (Nov. 26) (Dec. 8) 1888.

38. Walker, E. W. A.: *Proc. Roy. Soc., Lond.* **B89**:157 (Jan. 1) 1916.

For practical purposes their book of tables is cordially recommended as the best standard of weight available today. Evidence for this opinion will be given below.

The historical aspects of sitting-height and stem-length, and particularly the presumptive advantages of stem-length over stature, have been discussed by us previously.¹

NEW MATERIAL

The subjects studied were 114 pupils at Mr. Robert W. Rivers' Open Air School for Boys, a country day school in Brookline, just outside this city. We are indebted for the opportunity to the principal and also to the school physician, Dr. Richard M. Smith.

From the latter's two recent studies³⁹ on this establishment, it may be seen that our subjects represent a favored group, of American birth, good breeding and careful nurture.

Furthermore, the subnormal samples of boyhood discoverable, in process of betterment, in every school, have been in this study sifted out by means of the past history as obtained from parents, by the physical examination by the school doctor, by irregularity in school attendance and by general lack of stamina as observed from day to day by one of us who is in constant attendance as full-time school nurse.

Objection has been made to the use of well-to-do boys as criteria of the normal, on the ground that they are hot-house products (proteroplasia of Pfaundler⁴⁰). It seems to us, however, that either they must be regarded as the finest specimens of young hopefuls in the nation, or else we might as well discard breeding and physical culture as degenerative factors!

Measurements.—The observations were made on the chest, sitting height and stem length by one of us; while the stature and weight were taken by the other of us on the youngest boys, and by a master on the other boys. Age was noted to the nearest rather than the last birthday. Weights were taken to the nearest pound, heights to the nearest quarter-inch and chest-girth at nipple level, first at rest, then at full inspiration and finally after expiration. The average of these last two chest measurements seems preferable to the resting girth, as will be shown elsewhere. All measurements are net.

The records were made on 5x3 inch cards. It was found convenient to use Library Bureau No. 30-5003, after ruling in three extra vertical lines to subdivide into four parts the space for chest-girth; and one extra line toward the right side of the third column from the left to

39. Smith, R. M.: *Am. J. Dis. Child.* **18**:246 (Oct.) 1919; *Am. J. Dis. Child.* **20**:115 (Aug.) 1920.

40. Pfaundler, M.: *Ztschr. f. Kinderh.* **14**:1, 1916; **16**:85, 1917.

be used for sex. It would probably be more economical, and certainly more convenient, to have a card ruled to order by one of the card manufacturers, if one were planning to examine any large series of persons, say five hundred or more. A sample of the card as used is shown in Table 1.

TABLE 1. —RECORD CARD OF S. GANDI; MALE; AGED 7⁴¹

Date	No.	H	SI	λ	C				W	PW Lbs.	Error	
					R	Mx	Mn	M			Lbs.	%
3/2/21	R8	126 49½	69.5	69.0	57	61	55	58 22.8	49			
Ideal weight for chest (mean).....										45	4	8
Ideal weight for height.....										52	3	6
Ideal average of w for C and W for H.....										48.5	0.5	1
Von Pirquet weight for sitting-height (100).....										74	25	51
Von Pirquet weight for sitting-height (94).....										62	13	27
Dreyer-Hanson weight for stem.....										62	13	27
Dreyer-Hanson weight for chest (mean).....										48	1	2
Dreyer-Hanson weight for chest (rest).....										46	3	6
Dreyer-Hanson average of W for H and W for C (M).....										55	6	12
Dreyer-Hanson average of W for H and W for C (R).....										54	5	10

Abbreviations: No., serial number, e.g., Rikers School case 8; H, height standing, in cm. and inches; SI, sitting-height, in cm.; λ stem length, to nearest 0.5 cm.; C, chest-girth at nipple level, in cm.; R, chest-girth resting naturally; Mx, chest-girth after maximum expansion; Mn, chest-girth at minimum; M, chest-girth mean of last two measurements; W, weight observed; PW, predicted weight.

Method of Testing Standards.—In order now to ascertain which standard approaches most nearly to the observed weights of these healthy boys, we used the same simple though tedious procedure as in our earlier papers. In brief, we applied a given standard to a given boy, then took the difference between this theoretical weight and the subject's actual weight (which last was assumed to be the correct basis), and translated this difference in pounds from the observed weight into a percentage deviation or error. The formula was $(PW-W) \times 100/W$. For instance, if the predicted weight was 110 pounds and the weight 100 pounds, the difference of 10 pounds was recorded as a 10 per cent. prediction error. Calculation of this percentage is clearly necessary since, for example, the above 10 pounds absolute divergence is much less significant than it would be in the case of a child of 50 pounds, when the prediction error would be 20 per cent. By summing the errors thus calculated, and dividing through by the number of subjects measured we secured the average error of the prediction standard A. Standards B, C, etc., were similarly tested in turn.⁴²

41. The name, sex and age belong in the third, fourth and fifth columns of the card, but are here printed above in order to permit clearer display of the other columns.

42. Since this paper was submitted there have been printed several interesting discussions of Pirquet's method: Faber, H. K.: J. A. M. A. **77**:1837 (Dec. 3) 1921. Carter, W. E.: J. A. M. A. **77**:1911 (Dec. 10) 1921. Bardeen, C. R.: J. A. M. A. **77**:1988 (Dec. 17) 1921. Weymouth, F. W.: J. A. M. A. **77**:2080 (Dec. 24) 1921.

RESULTS OF TESTS

The numerical results are shown in Table 2 in the shape of various constants recommended by statisticians.

Our inferences from these facts are submitted, with the realization that they might be interpreted differently by those familiar with biometric principles.

1. The Ideal Tables, tentatively proposed by us elsewhere, show here the smallest average error, only 4.6 per cent.

2. At the same time, Dreyer and Hanson's tables show an accuracy only slightly less for children (mean error 4.8 per cent.), and for adult men are plainly the best standard available today (error 4.5 per cent., as published in an earlier article¹).

3. Dreyer and Hanson's tables also exhibit the smallest standard deviation of any method.

4. Also Dreyer and Hanson's range of error is the smallest of any.

TABLE 2.—ERROR IN PREDICTION OF WEIGHT BY DIFFERENT STANDARDS AS TESTED ON 114 RIVERS' SCHOOL BOYS

Rank in Order of Merit	Standard	Range	Mean	Stand- ard Devia- tion	Coeffi- cient of Varia- tion	Percentage of Times		
						Too High	Too Low	Cor- rect
1	Average of Ideal W for H and Ideal W for C.....	0 to 32	4.61	4.23	91.8	47	42	11
2	Average of Dreyer's W for stem and W for C (mean)	0 to 16	4.82	3.64	75.5	42	51	7
3	Average of Dreyer's W for stem and W for C (rest- ing).....	0 to 16	5.18	3.63	70.1	26	68	6
4	Dreyer's W for C (mean, nipple).....	0 to 19	5.41	4.14	76.5	37	54	9
5	Ideal W for C (mean, nipple)	0 to 18	5.94	4.11	69.2	40	53	7
6	Von Pirquet's W for Si (94).	0 to 28	6.52	1.66	25.5	55	49	10
7	Ideal W for H.....	0 to 50	7.10	6.79	95.6	53	40	7
8	Dreyer's W for stem.....	0 to 27	7.67	5.23	68.2	48	48	4
9	Dreyer's W for C (resting, nipple).....	0 to 26	8.04	5.12	63.7	15	81	4
10	Von Pirquet's W for sitting- height (100).....	0 to 53	21.5	10.0	46.5	98	1	1

* The name, sex and age belong in the third, fourth and fifth columns of the card, but are here printed above in order to permit clearer display of the other columns.

5. According to the coefficient of variability (C.V.), Dreyer and Hanson's tables excel our Ideal Tables, but the use of this criterion (C.V.) alone seems misleading, since the lowest C.V. of all pertains to Pirquet's formula, which we regard as the least useful of all those here analyzed. The difference in the results with Pirquet's formula is notable, according to whether one starts from an arbitrary index of 100 or 94.

6. Finally, as to theory, Dreyer's tables are said to be derived from a formula, and therefore represent a law rather than simply empiricism. This should mean that Dreyer's formula could be applied to individuals whose measurements lie outside the range of Dreyer and

Hanson's tables. It so happens, as detailed elsewhere,¹ that we have personally been unable to operate Dreyer's formula in such a way as to secure the values given in his tables, but this difficulty does not vitiate the value of the latter. Although we have not been able to use the formula for children outside the range of the tables, a graph made from the tables could probably be extended to give values for such small children.

CONCLUSIONS

Although our Ideal Tables seem the most exact by a slight margin, it is quite probable that for general use, on adults and children alike, the most satisfactory method hitherto proposed for estimating the correct weight of a normal person is the combination of Dreyer and Hanson's weight-for-stem and weight-for chest tables, with the modification that the chest-girth used be what we have called the mean girth rather than the resting girth advocated by Dreyer.

RESULTS FOLLOWING THE ADMINISTRATION OF
ALKALI PHOSPHATES TO SPASMOPHILIC,
RACHITIC AND NORMAL
INFANTS *

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AND
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Considerable research has been conducted recently, investigating the influence of the alkali phosphates, especially sodium and potassium diortho-phosphates, on normal and spasmophilic infants. Binger¹ produced tetany by the intravenous injection of ortho-phosphates. Howland and Marriott² found that when the inorganic phosphorus of the serum was high in severe nephritis that the calcium of the serum was greatly diminished. They considered the question, therefore, whether there was a sufficient accumulation of inorganic phosphates in the serum in tetany to account for the reduction of the calcium. Their determinations in cases of active tetany showed a low calcium content in the blood serum but no significant increase in phosphorus. Kramer, Tisdall and Howland^{2a} have very recently confirmed this work and state that an increase in the inorganic phosphorus of the serum does not seem to be responsible for infantile tetany, although in cases of rickets complicated by tetany there is a relatively high phosphate content (as compared with uncomplicated rickets), the significance of which is not as yet clear. Jones and Nye³ and Howland and Kramer⁴ have very recently found in normal infants that the concentration of calcium is from 9 to 11 mg. and inorganic phosphorus about 5 mg. per hundred c.c. of serum.

Jeppson and Klercker⁵ found that by the feeding of 0.20 gm. of phosphorus pentoxid per kilogram body weight to normal infants and 0.10 to latent spasmophilic infants, symptoms similar to those of active

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* From the Department of Pediatrics, University of Illinois and the Children's Department, Cook County Hospital.

1. Binger: *J. Pharmacol. & Exper. Therap.* **10**:105, 1917.

2. Howland, J., and Marriott, W. McK.: *Quart. J. M.* **11**:289, 1917.

2^a. Kramer, B.; Tisdall, F., and Howland, J.: *Am. J. Dis. Child.* **22**:431 (Nov.) 1921.

3. Jones, M., and Nye, L.: *J. Biol. Chem.* **47**:321, 1921.

4. Howland, J., and Kramer, B.: *Am. J. Dis. Child.* **22**:105 (Aug.) 1921.

5. Jeppson and Klercker: *Ztschr. f. Kinderh.* **28**:71, 1921.

spasmophilia were produced.⁶ These results were often evident in a few hours when the potassium salts were employed while larger quantities of sodium salts were needed. Often it required two or three days to produce symptoms with the latter. They conclude that especially during the first and second years, with the exception of the first few months of life, that an excess of alkali phosphates is received by most of the spasmophilic children. An 8 months old infant, weighing 8 kg., receiving 1 liter of cow's milk daily, will get from 0.25 to 0.3 gm. phosphorus pentoxid per kilogram. A large percentage of this will be in the form of alkali phosphates. These authors found that whey produced less irritation in latent spasmophilics when the phosphates had been precipitated and removed.

Howland and Kramer⁴ in a series of experiments found that the inorganic phosphorus of the serum is regularly reduced in active rickets, (except when complicated by tetany) sometimes to an extreme degree, and that by administering cod liver oil, the phosphorus content of the serum gradually rises to a normal figure and often somewhat above this. Sherman and Pappenheimer⁷ have reached the conclusion that lesions resembling rickets uniformly appeared in the absence, and were uniformly prevented by the presence of, sufficient phosphates in the diet. Similarly, Park⁸ and co-workers believe that the phosphate ion in the diet may be a determining factor for or against rickets. They found that if the phosphate content of the diet is sufficiently high, rickets-like changes in the skeleton do not occur in rats.

It is a well established fact that rickets and spasmophilia are very closely associated clinically. Very few cases of spasmophilia are observed which do not show evidences of rickets. In fact, Kassowitz and others have referred to spasmophilia as the nervous manifestation of rickets. According to our present knowledge it appears confusing to accept Jeppson and Klercker's view that an increased intake of phosphates alone is responsible for the precipitation of infantile tetany while a diminished phosphorus intake and content of the blood is a dominant factor in the development of rickets. The administration of cod liver oil and phosphorus prevents, arrests or cures both rickets and spasmophilia and yet increases the phosphorus content of the blood.

Because of these apparent discrepancies we made a number of observations on infants who were receiving various amounts of the

6. 0.20 gm. of phosphorus pentoxid (P_2O_5) represents in alkali diorthophosphates 0.27 gm. of potassium oxid (K_2O) and 0.18 gm. sodium oxid (Na_2O) or 0.49 gm. of potassium phosphate (K_2HPO_4) and 0.39 gm. of sodium phosphate (Na_2HPO_4).

7. Sherman, H. C., and Pappenheimer, A. M.: *Proc. Soc. Exper. Biol. & Med.* **18**:193, 1921.

8. Shipley, P. G.; Park, E. A.; McCollum, E. V.; Simmonds, N.: *Johns Hopkins Hosp. Bull.* **32**:160, 1921.

diortho-phosphates of sodium and potassium. A brief summary of the history and observations on these cases follows:

REPORT OF CASES

CASE 1.—G. D., aged 15 months, colored, weight 14 pounds, was admitted April 3, 1921, with evidence of an early bronchopneumonia and signs of active tetany, consisting of marked laryngospasm, Chvostek, Trousseau and an electrical reaction of 3.5 ma. with the C.O.C. There were signs of marked rickets. Calcium bromid, 5 grains, three times daily and cod liver oil with phosphorus, one dram three times daily were administered. Twelve days of this treatment brought the C.O.C. to 12 ma. April 15, and there were no signs of active tetany. Temperature was normal. Cod liver oil and calcium bromid were stopped and sodium chlorid, 15 grains, and potassium citrate, 10 grains, were given every morning. Six days later, April 21, the C.O.C. was 2.5 ma.; there was a definite Chvostek, a moderate Trousseau but no spontaneous carpopedal spasm. The sodium and potassium salts were then stopped and calcium lactate, 3 grains twice daily, cod liver oil with phosphorus, one dram three times daily and orange juice one ounce twice daily were begun. Six days later the C.O.C. was 15 + ma. No carpopedal spasm was present and there was merely a suggestion of a Chvostek.

May 27, 1921, the cod liver oil and phosphorus, calcium lactate and orange juice were discontinued and sodium diortho-phosphate, 17 grains, was given three times daily (a dosage amounting to 0.53 gm. per kg. in twenty-four hours) and continued until June 10. There were no signs of spasmophilia and the C.O.C. was 15 + ma. June 1, 1921, five days after beginning the administration of the phosphate, there were no signs of spasmophilia. June 8, 1921, there was no evidence of tetany, no diarrhea; cheerful, appetite and sleep normal. June 10, 1921 the phosphate was changed to the potassium salt and 0.53 gm. per kg. in twenty-four hours were given until June 14. There was no evidence of spasmophilia, the C.O.C. was 15 + ma. and the C.C.C. 8 ma. There was a moderate diarrhea. On June 11, 1921 the child was very irritable and restless. There were no clinical manifestations of tetany. The C.O.C. was 10 ma., the C.C.C. 3 ma. The diarrhea had subsided. June 13, the child was still irritable. The irritability for the past few days was discovered to have been due to cellulitis about the neck. June 14, 1921, the potassium diortho-phosphate was stopped and the cellulitis was treated. There was no evidence of spasmophilia and the C.O.C. was 15 ma. June 15, 18 and 20 there were no clinical manifestations of tetany and the electrical reactions were normal. June 20 the temperature was again normal and the infection practically cleared up.

This case shows that in spite of the presence of an acute infection, along with the administration of massive doses of phosphates, tetany was not induced. The moderate diarrhea probably due to the sodium salt was not aggravated by changing to the potassium salt.

CASE 2.—E. M., aged 3 years, colored, weight 17 pounds, was admitted May 23, 1921, suffering from pertussis, very marked rickets and active tetany, consisting of marked laryngospasm, Chvostek, Trousseau and C.O.C. of 4.5 ma., with generalized convulsions. She was placed on calcium lactate 5 grains three times daily; cod liver oil, 1 dram, and orange juice $\frac{1}{2}$ ounce, three times daily, in addition to antispasmodics and pertussis vaccine. June 2, there were still present signs of tetany, the C.O.C. was 4.5 ma. but the paroxysms of coughing were less frequent. June 10, the Chvostek sign was only suggestive; no Trousseau; C.O.C. 8 ma.; pertussis much less severe. June 14, no clinical evidence of spasmophilia and normal electrical reactions. June 19, developed measles but there were no signs of spasmophilia.

After complete recovery from the attack of measles July 15, 1921, the cod liver oil and calcium were stopped and potassium diortho-phosphate, 25 grains three times daily (0.62 gms. per kg. in twenty-four hours) was given for the following sixteen days. There were no signs of spasmophilia—the C.O.C. was 12 ma. and the C.C.C. 4 ma. July 18, no diarrhea or vomiting; cheerful; no signs of spasmophilia and electrical reactions normal. July 21, clinical record was the same, C.O.C. was 12 + ma. and C.C.C. 8 ma. The condition remained the same until the child was discharged July 31, 1921.

CASE 3.—M. M., twin of E. M., weight 18½ pounds, was admitted May 23, 1921, with the same condition as that of her sister. The findings were the same, except for the electrical reaction, which was C.O.C. 4 ma. The same treatment was instituted. June 2, the C.O.C. was 5 ma.; the Chvostek sign still present; paroxysms of coughing less frequent. June 7, practically the same. June 10, only a suggestion of a Chvostek; no other signs of tetany; C.O.C. 15 ma., C.C.C. 3 ma. June 19, the child developed measles, and there were no clinical signs of tetany.

After complete recovery from the attack of measles, the cod liver oil and calcium were stopped and potassium phosphate, 25 grains, three times daily (0.600 gm. per kg. in twenty-four hours) was begun July 5, and continued for six days. There were no signs of spasmophilia; the C.O.C. was 15 + ma., the C.C.C. was 5 ma. July 7, no vomiting or diarrhea, no signs of tetany; July 8, moderate diarrhea; no vomiting; no signs of tetany; the C.O.C. was 15 ma. and the C.C.C. 7 ma. July 10, discharged.

CASE 4.—F. D., 18 months of age, colored, weight 13 pounds, was admitted May 18, 1921, with malnutrition, marked rickets and no clinical manifestations of spasmophilia. May 23, sodium phosphate, 17 grains, three times daily (0.57 gm. per kg. per twenty-four hours) was given for seventeen days. June 1, there were no signs of tetany, the C.O.C. was 15 ma. June 5, the patient ate and slept well, no diarrhea and no clinical signs of tetany. June 8, the C.O.C. was 6 ma. but still there was no clinical evidence of tetany. June 9, the phosphate was changed to the potassium salt which was given in same dosage for the next eleven days. June 10, moderate diarrhea, no signs of spasmophilia. June 11, the C.O.C. was 5 ma.—no other definite signs of tetany. June 18 and June 20, electrical reaction C.O.C. 12 + ma. and no signs of tetany. Discharged.

CASE 5.—J. F., age 1 year, white, weight 16 pounds, was admitted April 29, 1921, with furunculosis, no signs of spasmophilia and only moderate rickets. The furunculosis cleared up, and May 23, sodium phosphate, 19 grains, three times daily (0.52 gm. per kg.) was given for eleven days. The C.O.C. was 15 ma. June 1, still no evidence of spasmophilia, the C.O.C. was 12 ma. June 7, developed an acute encephalitis; no evidence of tetany. Died of acute infection one week later.

CASE 6.—J. L., aged 8 months, white, weight 12 pounds, was admitted June 6, 1921, with malnutrition and no evidence of rickets. June 10, sodium phosphate, 17 grains, three times daily, was given (0.62 gm. per kg. per twenty-four hours). The C.O.C. was 15 ma.; the C.C.C. was 3.5 ma. After being on this preparation for about four days the electrical reaction was unchanged and there were no clinical manifestations of spasmophilia.

CONCLUSIONS

1. The administration of from 0.55 to 0.60 gm. of potassium diorthophosphate (K_2HPO_4) or sodium diorthophosphate (Na_2HPO_4) per kilo body weight per twenty-four hours to the infants neither activated latent spasmophilia nor produced symptoms resembling

spasmophilia. In one case of rickets the electrical excitability approached the spasmophilic reaction for about thirty-six hours although no other manifestations of tetany were present notwithstanding the fact that the potassium phosphate was continued.

2. Several of the cases selected were at the most susceptible age for spasmophilia to develop.

3. Several of the infants showed marked evidences of rickets, supposedly making them more prone to develop spasmophilia.

4. Even the superimposing of acute intercurrent infections in a number of cases, plus the administration of the phosphates did not precipitate spasmophilic manifestations.

5. Three of the patients had just recovered from active spasmophilia and yet it could not be reprecipitated by administering the phosphates.

6. These patients had recovered from the active spasmophilia rapidly on receiving phosphorized cod liver oil, which is known to increase the phosphorus content of the blood.

7. It is evident, therefore, that the most susceptible cases which could be selected did not develop spasmophilia when placed on large doses of diorthophosphates and so we are unable to confirm the results of Jeppson and Klercker.

We wish to express our sincere thanks to Dr. Julius H. Hess for suggesting this research, for his kindly interest and the opportunity of reporting cases from his ward.

STUDIES OF INFANT FEEDING XVI

A BACTERIOLOGIC STUDY OF THE FECES AND THE FOOD OF NORMAL BABIES RECEIVING BREAST MILK *

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INTRODUCTION

Much has been said concerning the intestinal flora of infants, both breast fed and bottle fed, but owing to the intangibility of certain aspects of the subject, the field seems to be open to further investigation.

Description of the bacteriology of breast fed babies' stools which have been published heretofore are based chiefly on small groups, on very young infants in maternity wards, or on diseased babies. In the Research Laboratories of The Boston Floating Hospital, during the past year, we have had an unusual opportunity in connection with certain metabolism investigations for studying a fairly large group of normal breast fed babies of different ages.

The work here described has been undertaken as an independent research subject although no claims are made as to its originality. Its chief aim has been to obtain complete bacteriologic data as a parallel to metabolism work done simultaneously on the same babies.

With the idea of obtaining as complete data as possible concerning the source of intestinal bacteria, samples of the breast milk which the babies were receiving were examined bacteriologically also, in an effort to determine, if possible, what relationship there might be between the bacteria in breast milk as fed to normal babies and the fecal flora of the same babies.

During our investigation a "bifidus-like" bacillus was isolated from the breast milk and from the skin around the nipple. It is a pleomorphic slender bacillus exhibiting on artificial mediums, under various conditions, forked forms, clubbed forms, V and Y forms, crossed forms, coccal forms and straight or slightly curved forms generally in parallel arrangement. In young cultures and in rapidly growing cultures the organisms are usually gram-positive.

On one occasion definite spores were seen when stained by the Ziehl-Neelsen method. After heating cultures to 80 C. for ten minutes a feeble growth could usually be obtained but a longer exposure prevented growth.

* Received for publication Nov. 2, 1921.

* From The Boston Floating Hospital Laboratories.

The bacillus was isolated only under aerobic conditions but in the second generation on artificial mediums it grew almost as well anaerobically. Culturally, it ferments, without gas, dextrose, saccharose, lactose, maltose, raffinose and mannite but grows very poorly in mannite medium. Milk is clotted very slightly.

Because of its typical morphology and its similarity in other respects to the descriptions of *B. bifidus* by preceding investigators, we do not hesitate to call this organism *B. bifidus* also. It differs from *B. bifidus* as isolated from nurslings' feces in one respect only, namely, its ability to grow well initially under aerobic conditions. One would expect that an organism which had existed on the skin would thrive in the presence of oxygen.

As the result of our investigations we believe that the *B. bifidus* which is present in or on the mother's nipple is an important source of the bifidus organisms found in the nursling's intestine. The reason for their predominance in the nursling's feces has been explained adequately by Kendall and preceding investigators. In their passage through the intestinal tract the bacilli have had to adapt themselves to increasingly anaerobic conditions so that as a fecal organism *B. bifidus* is a voluntary, though not necessarily a strict anerobe. Because of its sensitiveness to environmental changes it is difficult to cultivate artificially.

One of our reasons for believing that this organism which we have isolated from breast milk is a predecessor of the fecal *B. bifidus* is that after anaerobic cultivation in milk digested by intestinal ferments a straight slender rod, morphologically typical of *B. bifidus* as it appears in direct smears from the feces, resulted.

After going over the available literature we find that several other investigators have been able to cultivate *B. bifidus* aerobically. Noguchi¹ believes that this organism has an aerobic phase, and Howe² has been able to obtain good aerobic cultures of his organisms isolated from carious teeth. Torrey,³ by using a special method, has also succeeded in aerobic cultivation.

We can find no definite statement in the literature as to the isolation of *B. bifidus* from breast milk. The majority of writers⁴ are interested only in pathogenic cocci, although several mention finding occasionally a slender bacillus to which no further allusion is made.

Escherich⁵ made cultures from women's milk but was apparently more interested in the numbers than in the types of bacteria present.

1. Noguchi: J. Exper. M. **12**:182, 1910.

2. Howe: J. M. Research, N. S. **31**:481, 1917.

3. Torrey: J. Bacteriol. **2**:435, 1917.

4. Koestlin: Arch. f. Gynäk. **3**:201, 1897.

5. Escherich: Fortschr. f. Med. **3**:231, 1885.

The following year, however,⁶ he offered the supposition that lactic acid bacilli may be among the adventitious types entering the intestines before the first nursing or that they may develop on the nipples or in the milk that remains in the baby's mouth.

Moro⁷ states that it is easy to obtain *B. acidophilus* from breast milk on beerwort agar. At that time he considered *B. acidophilus* the predominant organism in nurslings' stools, but later⁸ he corrected this statement, charging himself with the neglect of anaerobic methods whereby he failed to isolate *B. bifidus* as the predominant organism. While he corrects his work on the fecal flora he does not speak here about the organism which he isolated from breast milk as *B. acidophilus*. However, from his later description of *B. bifidus*, which he considers a very polymorphic, strictly anaerobic bacillus, one may assume that he did not isolate *B. bifidus* as such from breast milk.

Noguchi¹ considers the breast of the mother one source of *B. bifidus* in the stools of breast fed babies. He thinks that in its aerobic phase the organism may inhabit the breast and skin of the mother and that the anaerobic phase also is met with in the nursling's feces as *B. bifidus communis* (Tissier). This is somewhat parallel to our belief but while his aerobic organism resembles a simple spore bearer, ours has all the morphologic characteristics of the fecal *B. bifidus*.

A STUDY OF THE FECAL FLORA

The babies selected were nurslings whose physical examinations rated them as normal infants. The bacteriologic investigations were made on sixty-five specimens from thirty-eight babies; one specimen was examined after admission to the ward and another, in the majority of cases, at the end of the metabolism period.

The thirty-eight babies ranged in age from 2 days to 6 months. Of these, twenty-eight had received only breast milk since birth and the other ten had had some cow's milk. All babies who had received cow's milk were placed on a strict breast milk diet after admission.

In spite of our efforts to use only breast fed babies, six orphans from St. Mary's Infant Asylum and four breast fed babies who had previously received some cow's milk, were included by mistake. However, the mistake was a happy one in that it offered several points of comparison.

The routine procedure consisted of the examination of direct smears and of aerobic and anaerobic cultures from the feces. The specimens were obtained by rectal tube and sent directly to the laboratory, where smears and cultures were made immediately.

6. Escherich: Die Darmbakterien des Säuglings, 1886.

7. Moro: Jahrb. f. Kinderh. 2:38, 1900.

8. Moro: Jahrb. f. Kinderh. 11:687, 1905.

About 1 gram of feces was emulsified in 10 c.c. of sterile physiologic solution of sodium chlorid and from this suspension the smears and cultures were made. For the study of aerobic organisms Endo plates or lactose litmus agar plates were used and colonies finished for identification by cultural reactions in carbohydrate and other mediums. For the anaerobic work dextrose or lactose agar slants were inoculated and incubated in vacuum bottles after Stitt's method with slight alterations.

Direct Smears.—Of the strictly breast fed babies, all but three showed either a practically pure growth of *B. bifidus* in the direct smears or a large predominance of this organism with only a few cocci and gram-negative bacilli. A few spore bearers were observed in almost all cases. The three exceptions were:

No. 35, whose smear showed a large predominance of gram-negative bacilli, was having loose stools at the time her second specimen was taken. Since *B. alkaligenes* was isolated in unusually large numbers by aerobic culture she presumably was having an intestinal upset. Her first specimen seven days before was typical of the other breast fed babies.

No. 43 had an unusually large number of sporebearers. This organism was typical of *B. aerogenes capsulatus* and did not appear in the aerobic cultures.

No. 57 had many gram-negative bacilli. She had been having enemas for several days before the specimen was taken which presumably eliminated these organisms more quickly than normally.

Of the ten babies who had received some cow's milk:

No. 38, after nine days on a strict breast milk diet showed a direct smear typical of a breast fed baby. He had been entirely breast fed for two weeks after birth and had received cow's milk alone for three or four days.

Nos. 39 and 40, who had received supplementary feedings of cow's milk since birth because their mothers had an inadequate supply, showed a high percentage of gram-negative bacilli after nine and sixteen days, respectively, on a strict breast milk diet.

No. 41 had received supplementary feedings of cow's milk in addition to the breast but a direct smear from her stool showed a practically pure growth of *B. bifidus* after sixteen days of straight breast milk.

No. 44 had received cow's milk just one day, but was only eight days old when a specimen of feces was examined. Her direct smear showed a fairly high percentage of cocci and gram-negative bacilli. Probably she was still at the transitional stage described by Kendall⁹ which bridges the period of early adventitious bacterial infection of the intestinal tract to the period of the dominant breast milk flora.

No. 45 had received cow's milk for several days before admission and three weeks later still showed a high percentage of gram-negative bacilli.

No. 54 had received cow's milk alone for three or four days before admission. There was no history of the previous feeding. At the beginning of the fourth week the direct smear from this case still showed a high percentage of cocci and gram-negative bacilli in spite of a continuous breast milk diet.

9. Kendall: Bacteriology, p. 581.

No. 55 had received cow's milk alone for the first week after birth. After seven days of a strict breast milk diet his direct smear showed only gram-negative bacilli. Five days later *B. bifidus* began to predominate but the percentage of colon-like bacilli was still high.

No. 58 was an interesting case. She was only two days old when admitted and had received cow's milk for twenty-four hours. When the first specimen from this baby was examined the stool was still a meconium stool, and, as was to be expected, contained many cocci and gram-negative bacilli. Since she was started on a breast milk diet at the end of her second day this baby was practically on the same basis of feeding as a breast fed baby. The feces examined eight days later contained a flora typical of a breast fed baby, as indicated by the direct smear. Apparently the small amount of cow's milk ingested during a period of physiologic adjustment had no permanent effect.

No. 59 was two weeks old when admitted. There was no history of feeding prior to admission to St. Mary's Asylum but she received cow's milk alone for several days at that institution. The first specimen examined after four days on drawn breast milk showed a proportion of cocci and gram-negative bacilli larger than in the direct smears of the normal breast fed babies. A second and third specimen examined at intervals of eight days showed a continual reduction of these organisms, but it was not until the fourth week that a flora absolutely typical of a breast fed baby was established.

Anaerobic Cultures.—Unquestionably a large number of the bacteria present in the feces are dead but it is of interest to know whether the bifidus type survives the last period of intestinal existence in as high a percentage as the direct smears seem to indicate.

Therefore, the chief aim of this anaerobic study has been to find a culture method which would give an approximate estimate of the living bacterial types naturally present in the feces of normal nurslings.

Since *B. bifidus* is generally considered an obligate anaerobe and since the other types of bacteria ordinarily found in such feces, as *B. coli*, *B. lactis aerogenes*, *M. ovalis* and staphylococci, are all facultative anaerobes and may grow well under anaerobic conditions it was logical to assume that proper anaerobic cultivation would offer an environment to all the above types as suitable as that part of the intestine where they had passed the last period of their metabolism.

After trying out various anaerobic methods, the most uniform results were obtained by altering slightly Stitt's vacuum bottle method. Dextrose and lactose agar slants were used instead of stab cultures except for isolation work. By omitting the layer of liquid petrolatum and leaving the plugs out of the tubes a high degree of anaerobiosis was insured.

This corroborates the work of Gates and Olitsky¹⁰ and of Ivan Hall¹¹ who have concluded, after careful investigation, that the layer of oil is inefficient in procuring anaerobic conditions. We also agree

10. Gates and Olitsky: J. Exper. M. **33**:51 (Jan.) 1921.

11. Hall: J. Bacteriol. **6**:1 (Jan.) 1921.

TABLE I.—STUDY OF THE FECAL FLORA OF INFANTS *

Baby	Admission Age	Feeding Before Admission	Feeding After Admission	Specimen	Days After Admission	Proportion of Bacterial Types in			Remarks
						Direct Smear	Anaerobic Culture	Aerobic Culture	
35	8 weeks	Breast	Breast	1	4	Bifidus Few colon-like	B. coli Few staphylococci	Tendency to loose stools
				2	11	Colon-like Few bifidus Rare coccus	B. alkaligenes Few B. subtilis Rare diplococcus	
36	2 months	Breast	Breast	1	9	Bifidus Few colon-like Rare coccus	B. coli Few M. ovalls Few paratyphoid-like	
37	4 months	Breast	Breast	1	2	Bifidus Few cocci	B. pyocyaneus Few B. coli	Specimen left in ward over night
				2	9	Bifidus Few colon-like Rare coccus	B. coli Few M. ovalls	
38 St. M.	3 weeks	Breast; cow's milk 3-4 days	Drawn breast milk	1	9	Bifidus Few colon-like Few cocci	B. coli Rare M. ovalls Rare B. pyocyaneus	Cow's milk formula made up with lactose
				2	16	Bifidus Few colon-like Few cocci	B. coli Few pyocyaneus	
39	16 days	Breast; cow's milk supplementary	Breast; drawn breast milk	1	9	Bifidus Many colon-like	B. coli Rare staphylococcus	Mother's milk inadequate
40	6½ weeks	Breast; cow's milk supplementary	Breast; drawn breast milk	1	16	Bifidus Many colon-like Few spore bearers Rare coccus	B. coli	Mother's milk inadequate
41	6½ weeks	Breast; cow's milk supplementary	Breast; drawn breast milk	1	16	Bifidus	B. coli	
42	5½ weeks	Breast	Breast	1	6	Bifidus	B. lactis aerogenes Many staphylococci	
43	3½ months	Breast	Breast	1	3	Bifidus Many spore bearers Few cocci Rare colon-like	B. coli Few B. lactis aerogenes	No clinical evidence for prominent spore bearer
				2	8	Bifidus Spore bearer Few cocci	B. coli Few M. ovalls Rare B. alkaligenes Rare B. megathierum	

* Explanation of Table 1: Predominant organism stands first without modification. "Colon-like" by cultural tests are *B. coli* in most cases, *B. lactis aerogenes* in a few, and *B. alkaligenes* in one. Since the chief aim was to determine the proportion of types the group name rather than the name of the individual organisms has been noted more especially.

44	8 days	Breast; cow's milk	Drawn breast milk	1	Same day	Bifidus Moderate number of colon-like cocci	B. coli B. lactis aerogenes Few staphylococci Few M. ovalis Few yeast B. coli Few M. ovalis	
45	5 days	Breast; cow's milk	Drawn breast milk	1	21	Bifidus Many colon-like Few cocci	B. coli	
48	4 weeks	Breast	Breast	1	2	Bifidus Few cocci Rare colon-like	B. coli Rare B. subtilis Rare staphylococci	
				2	7	B. coli Few B. lactis aerogenes	
49	1 month	Breast	Breast; drawn breast milk	1	4	Bifidus	B. coli	
				2	9	Bifidus Few colon-like Rare cocci	Staphylococcus Many M. ovalis Few B. cloacae	Frequent loose stools for 5 days previous
50	6 months	Breast	Breast	1	5	Bifidus	B. coli Few staphylococci	
				2	14	Bifidus Few spore bearers Few cocci Rare colon-like	B. coli Rare staphylococci	
52	1 month	Breast	Breast	1	7	Bifidus	B. coli Rare staphylococci	
54	1 week	Breast	Drawn	1	7	Bifidus Moderate number of colon-like cocci	B. coli Few staphylococci	
				2	12	Bifidus Many colon-like Many cocci	B. coli Many B. lactis aerogenes	
55	1 week	Cow's milk	Drawn breast milk	1	7	Colon-like	B. lactis aerogenes Many yeast Many B. coli	No history of any breast feeding
				2	12	Bifidus Many colon-like	Bifidus Small number of M. ovalis	B. coli B. lactis aerogenes	

TABLE 1.—STUDY OF THE FECAL FLORA OF INFANTS.—(Continued)

Baby	Admission Age	Feeding Before Admission	Feeding After Admission	Specimen	Days After Admission	Proportion of Bacterial Types in			Remarks
						Direct Smear	Anaerobic Culture	Aerobic Culture	
57	6 weeks	Breast	Breast; drawn breast milk	1	8	Bifidus Many colon-like Rare coccus	B. coli	Enemas for several days before taking specimen
58	2 days	Cow's milk (24 hours)	Drawn breast milk	1	2	Bifidus Many cocci Many colon-like	Colon-like Many staphylococci Occasional bifidus	B. coli	Still a meconium stool
59 St. M.	2 weeks	? Cow's milk (2 days)	Drawn breast milk	2	10	Bifidus Few colon-like	Colon-like Many bifidus	B. coli Few M. ovals Few diplococci	No history of feeding before admission to St. Mary's
				1	4	Bifidus Many colon-like Many cocci	Bifidus Many colon-like Many cocci	B. coli Many diplococci	
				2	22	Bifidus Moderate number of colon-like Occasional coccus	Bifidus Colon-like M. ovals	B. lactis aerogenes Few B. coli	
				3	30	Bifidus Small number of colon-like Few cocci	Colon-like Many M. ovals Few bifidus	B. coli Few M. ovals Few staphylococci	
60	8 weeks	Breast	Breast	4	38	Bifidus Few colon-like	Bifidus Many colon-like Few yeasts Few cocci	B. coli	
61	1 month	Breast	Breast; drawn breast milk	1	2	Bifidus Few colon-like Few cocci	Bifidus Few colon-like	B. coli	Mother's milk inadequate
62	1 month	Breast	Breast; drawn breast milk	1	1	Bifidus Small number colon-like Few cocci	B. coli Many diplococci Moderate number B. aerogenes M. ovals B. coli Rare staphylococci	Mother had follicular tonsillitis and caked breast Mother recovered
				2	9	Bifidus Few colon-like Few cocci	Bifidus Many colon-like		
				1	1	Bifidus	Staphylococci only	
				2	19	Bifidus Rare colon-like Rare coccus	Bifidus Many colon-like	B. coli Rare staphylococci	

63	1 month	Breast	Breast	1	2	Bifidus	Bifidus Many colon-like Rare coccus	B. coli Occasional M. ovals	
65	5 weeks	Breast	Breast	1	1	Bifidus Few cocci Rare colon-like	Bifidus Many colon-like Few cocci	B. coli Many M. ovals	Mother had acute respiratory infection
66	16 days	Breast	Breast	1	5	Bifidus Many colon-like Few spore bearers Rare coccus	Bifidus Many colon-like Few cocci	B. coli Rare staphylococci	Five to seven loose stools daily
67	5 weeks	Breast	Breast	1	2	Bifidus	Bifidus Moderate number colon-like	B. coli Many yeast Few dewdrop colonies not growing on Endo after flabing, perhaps diphtheria	
68	2 months	Breast	Breast	1	Same day 7	Bifidus	Bifidus Many colon-like	B. coli Many M. ovals Few staphylococci	Eight days after admission mother and baby had positive diphtheria cultures
69	2 weeks	Breast	Breast	1	Same day	Bifidus	Bifidus Many colon-like Few yeasts Few M. ovals	B. coli Few B. alkaligenes Few staphylococci	
70	6 months	Breast	Breast	1	2	Bifidus	Bifidus Many colon-like Many cocci	B. coli Many M. ovals	
				2	12	Bifidus Rare colon-like	Bifidus		

TABLE 1.—STUDY OF THE FECAL FLORA OF INFANTS.—(Continued)

Baby	Admission Age	Feeding Before Admission	Feeding After Admission	Specimen	Days After Admission	Proportion of Bacterial Types in			Remarks
						Direct Smear	Anaerobic Culture	Aerobic Culture	
71	1 month	Breast	Breast	1	1	Bifidus	B. coli Few M. ovals	
				2	25	Bifidus	B. coli Few M. ovals	
72	6 weeks	Breast	Breast	1	Same day	Bifidus	Bifidus Many colon-like	B. coli Few M. ovals Few staphylococci	
				2	8	Bifidus Few cocci	Bifidus Many cocci Few colon-like	B. coli Many staphylococci Many M. ovals	
74	2 weeks	Breast	Breast	1	1	Bifidus Rare colon-like Rare cocci	Bifidus Many colon-like Few M. ovals	B. coli Moderate number M. ovals and staphylococci	
				2	8	Bifidus Rare colon-like			
75	18 days	Breast	Breast	1	1	Bifidus	Bifidus cocci Many colon-like	B. coli Many staphylococci Many yeast	
				2	12	Bifidus	Bifidus	B. coli Many yeast Few M. ovals	
77	19 days	Breast	Breast	1	1	Bifidus	Bifidus	B. coli Few M. ovals	
				2	8	Bifidus	Bifidus Many colon-like Few cocci		
79	14 days	Breast	Breast	1	1	Bifidus			
				1	1	Bifidus			
81	Breast	Breast	1	1	Bifidus			
				1	1	Bifidus			

with Hall that the old Buchner method is more successful if the inoculated tubes are left unplugged.

The above investigators have had illuminating results with methylene blue as an indicator of the degree of anaerobiosis. The use of this is dependent on so many factors that it is rather complex for ordinary work. However, it is advantageous to have some way of determining the degree of anaerobiosis so in this work a culture of *B. pyocyaneus* was used which produced a large amount of pigment in the presence of free oxygen but did not produce any pigment under anaerobic conditions.

In this study the use of solid medium had an advantage over liquid mediums since the colonies could be seen growing and therefore definitely represented living bacteria.

Everyone who has tried to cultivate these fecal organisms has spoken of the fact that the bifidus type is quickly crowded out by the other bacteria, *M. ovalis* and a yeast seeming to be the chief offenders in this respect. While it is undoubtedly true that artificial mediums offer a chemical environment more favorable to these organisms, a careful study of the colonies in these fecal cultures seemed to indicate that the antagonism was due to physical as well as chemical factors. The bifidus colonies are so much smaller and slower growing than those of the other types that the latter soon use all the available space on the surface of the medium, incidentally choking out the former. In diluted cultures the bifidus organisms multiply very well so long as there is space in which to proliferate. They also grow better under these conditions in symbiosis with the other bacteria than when isolated.

As may be seen in Table 1, all except five of the twenty-eight specimens examined by anaerobic cultures showed a large predominance of the bifidus group, as did the direct smears from these specimens. The five exceptions were as follows:

No. 58, in which gram-negative bacilli were predominant, staphylococci prominent and *B. bifidus* scantily represented. The direct smear from the same specimen showed a slight predominance of *B. bifidus* but since this was a meconium stool presumably the bifidus type had not established itself strongly.

No. 58.2 was the same case eight days later, but here the bifidus organisms were present in large numbers even though the colon type was still predominant; showing the gradual transition to the dominance of *B. bifidus* after a continuous breast milk diet.

Nos. 59.2 and 59.3 showed a large number of cocci and gram-negative bacilli as compared with the bifidus type. This baby had been on a cow's milk diet and its direct smears did not present the picture typical of a normal breast milk stool.

No. 75.1. The direct smear from this specimen showed practically a pure growth of the bifidus type. In the anaerobic culture cocci rivalled the bifidus organisms strongly. This was a strictly breast fed baby but the mother had been having nipple trouble which may have been the cause of a coccus infection. There were also many staphylococci found in the aerobic cultures.

Aerobic Cultures.—Of fifty specimens examined by aerobic culture all but four showed a predominance of the *B. coli*-*B. aerogenes* types. The four exceptions were:

No. 35.2, which showed a predominance of *B. alkaligenes*. At the time this specimen was examined the child was having loose stools. The direct smear also showed a predominantly gram-negative flora.

No. 37.1. This specimen was left in the ward over night and when plated showed a predominance of *B. pyocyaneus*.

No. 49.2. This baby, whose culture showed a predominance of staphylococci, had been having from five to seven loose stools for five days previous to the examination of this specimen. The increased peristalsis probably let free a larger number of living staphylococci than normally.

No. 62.1. In this specimen staphylococci only were found on the aerobic plates; the indication that there must have been an influx of staphylococci into the intestinal tract great enough to antagonize the prominent *B. coli*-*B. aerogenes* types. This was unquestionably true, for the baby had an infection of the nasal pharynx and the mother a definite follicular tonsillitis and an acute mastitis at the time the fecal specimen was examined.

A BACTERIOLOGIC STUDY OF BREAST MILK

The investigation here reported is divided into two parts.

Do the So-Called Adventitious Organisms Found in the Breast Milk Appear in the Feces?—The investigation first started in to discover how many of the so-called adventitious organisms found in the milk passed through the intestinal tract and appeared in the feces. This work was all done on samples of drawn breast milk which had been collected under the supervision of Miss Martha H. Stark of the On Shore Department of The Boston Floating Hospital and was to be used for supplementary bottle feedings. It was brought to the hospital in sterile bottles, kept on ice, and used in the order of arrival. This type of milk was used for this part of our investigation since it might be expected to contain more adventitious bacteria than milk which had been directly drawn from the breast and which had not been handled.

Fifty-four samples of drawn breast milk used to feed the babies enumerated in Table 1 were examined bacteriologically in this part of the investigation, forty by aerobic cultivation only and the other fourteen by anaerobic cultures in addition. The samples were examined before and during the metabolism period of the babies using the milk.

The supplementary feedings for the babies whose mothers had an inadequate amount of breast milk and the entire feedings for the orphans from St. Mary's were made up by mixing an adequate amount of the oldest milk of the supply on hand. When taken in the feedings, 75 per cent. of this milk was forty-eight hours old, 5 per cent. was seventy-two hours old, and the other 20 per cent. was from twelve to forty-eight hours old. Plated on ordinary agar, the different milks gave counts ranging from 10 to 150,000 bacteria in one cubic centimeter.

TABLE 2.—STUDY OF INTESTINAL FLORA OF STRICTLY BREAST FED BABIES

Baby	Type of Feeding Before Admission	Admission Age	Period of Receiving Supplementary Breast Milk*	Organisms Isolated from This Milk During This Period	Organisms Found in Feces at End of This Period	Remarks
38	Breast fed 2½ weeks; cow's milk 3-4 days	3 weeks	16 days	<i>B. coli</i> <i>Staphylococci</i> <i>B. pyocyaneus</i> (1 sample)	<i>B. bifidus</i> <i>B. coli</i> <i>M. ovalis</i> <i>B. pyocyaneus</i>	It is hard to say whether the <i>B. pyocyaneus</i> in the feces had any relationship to that found in the breast milk 3 days before since this baby had had cow's milk before admission and <i>B. pyocyaneus</i> was isolated from a previous stool
39	Breast fed; cow's milk (supplementary)	16 days	9 days	<i>B. coli</i> <i>Staphylococci</i> <i>B. pyocyaneus</i> (1 sample)	<i>B. bifidus</i> <i>B. coli</i> <i>Staphylococci</i>	
40	Breast fed; cow's milk (supplementary)	6½ weeks	16 days	<i>B. coli</i> <i>Staphylococci</i> <i>B. pyocyaneus</i> (1 sample) <i>B. subtilis</i> (1 sample)	<i>B. bifidus</i> <i>B. coli</i> <i>Staphylococci</i> Spore bearer	A few sporogenous bacilli were seen in the direct fecal smear which did not appear in aerobic culture. It is a question whether these resulted from the ingestion of breast milk containing <i>B. subtilis</i> 6 days before or whether they came from the previous cow's milk formula or perhaps from a source outside the food
41	Breast fed; cow's milk (supplementary)	6½ weeks	6 days	<i>B. coli</i> <i>Staphylococci</i> <i>B. pyocyaneus</i> (1 sample) <i>B. subtilis</i> (1 sample)	<i>B. bifidus</i> <i>B. coli</i>	
54	Breast fed originally; cow's milk entirely for several days	1 week	12 days	<i>B. coli</i> <i>Staphylococci</i> <i>B. subtilis</i>	<i>B. bifidus</i> <i>B. coli</i> <i>B. lactis aerogenes</i>	
55	No history of breast feeding; cow's milk entirely	1 week	12 days	<i>B. coli</i> <i>Staphylococci</i> <i>B. subtilis</i>	<i>B. bifidus</i> <i>B. coli</i> <i>B. lactis aerogenes</i>	
57	6 weeks	<i>B. coli</i> <i>Staphylococci</i> <i>B. subtilis</i>	<i>B. bifidus</i> <i>B. coli</i> Cocci	

* All samples of breast milk contained staphylococci.

Since *B. Coli* and staphylococci are universally considered obligate inhabitants of the digestive tract it is of little value at this point to discuss the part which the *B. Coli* and the staphylococci found in the milk may have played in determining the fecal flora in these cases. As to the so-called adventitious *B. subtilis* and *B. pyocyaneus* isolated in small numbers from these samples of milk the relationship is little

clearer since the parallel specimens of feces containing these organisms were from babies who had previously received a cow's milk formula. However, Cases 40 and 41 were absolutely parallel in age, in type of feeding previous to admission, and in the feedings received in this hospital. If the bacteria of the food alone determined the bacteria of the feces one might expect both babies to have exactly the same fecal flora. During the course of these examinations several lots of breast milk were examined from mothers in the hospital who were contributing occasionally to the general supply since they had more milk than was needed for their own babies. It was noticed that the bacterial count of these samples was low and that the only organisms isolated were staphylococci. These specimens were collected with aseptic precautions. Comparing them with the milk obtained from outside sources brought out the fact that even a slight amount of handling may introduce adventitious bacteria into the feedings of infants receiving breast milk from a bottle.

What Bacteria May Enter the Baby's Mouth During Nursing.—The second part of the investigation dealt specifically with the kind of bacteria which may enter a baby's mouth directly from the breast. Six mothers in the hospital contributed entirely to this work.

In order to find out what types of organisms may naturally enter a baby's mouth directly from the breast it was decided to work only with mothers here in the hospital where the greatest aseptic precautions could be taken. The chief point of interest was to see if *B. bifidus* could be isolated from breast milk since it occupies such a prominent place in the fecal flora of normal breast fed babies. An attempt was made to obtain specimens of breast milk with as little handling as possible. Since it was realized that the skin around the area of the nipple must be a factor in contaminating the milk as it enters the baby's mouth, swabs from this area were made in all cases. The method of obtaining both milk and swab specimens was as follows:

Immediately before nursing time the area of the nipple was swabbed with a sterile swab soaked in sterile salt solution. The swab was then returned to its sterile test tube. Next the breast was wiped off with boric acid solution and about 10 c.c. milk was withdrawn by means of a sterile breast pump. The milk was evacuated very carefully into a sterile tube. After nursing a second specimen was obtained in similar fashion. Specimens from six mothers were obtained in this way (Table 3).

Lactose litmus agar plates were used for the aerobic cultivation of the first three specimens and dextrose agar slants for the anaerobic cultures. For the second three specimens dextrose agar slants for aerobic cultivation were used in addition. As soon as the specimens

reached the laboratory they were plated and smeared. They were kept for two weeks after this at room temperature, carefully protected from dust, and cultured and smeared at regular intervals. These later cultures failed to add any further information.

The organisms described as "bifidus-like" were morphologically typical of *B. bifidus* in subcultures isolated from stools.

TABLE 3.—STUDY OF INTESTINAL FLORA BEFORE AND AFTER NURSING

Specimen	Aerobic Cultivation			Anaerobic Cultivation		
	Before Nursing Milk 1	Nipple Swab	After Nursing Milk 2	Before Nursing Milk 1	Nipple Swab	After Nursing Milk 2
1	Cocci only good growth	Staphylococci only	Cocci only scanty growth	Cocci only fair growth	Staphylococci only	Cocci only scanty growth
2	Cocci only good growth	Staphylococci good growth <i>B. subtilis</i> rare colony	Cocci only scanty growth	Cocci only fair growth	Staphylococci only	Cocci only scanty growth
3	Cocci only good growth	Staphylococci Bifidus-like organism*	Cocci only scanty growth	Cocci only fair growth	Staphylococci only	Cocci only scanty growth
4	Cocci fair growth Bifidus-like organism† rare colony	Cocci only	Cocci only scanty growth	Cocci only fair growth	Cocci only	Cocci only scanty growth
5	Cocci good growth Bifidus-like organism‡ good growth	Cocci only	Omitted	No organisms of definite morphology	No growth	Omitted
6	Cocci Bifidus-like organism§ good growth	Cocci Bifidus-like organism§	Omitted	No organisms of definite morphology	Cocci only	Omitted

* Isolated from aerobic lactose litmus agar plates. Subcultures grew poorly and soon died out but finding this organism gave impetus to the work and the last three specimens were examined even more carefully.

† Isolated from aerobic dextrose agar slant, after 24 hours' incubation. Rather attenuated and died out after several generations.

‡ Isolated from aerobic dextrose agar slant after 48 hours' incubation. Subcultures showed good growth and were kept for future study.

§ Isolated from aerobic lactose litmus agar plates after three days' incubation. Also from aerobic dextrose agar slant after four days' incubation. Good subcultures kept for future study.

CONCLUSIONS

Bacteriology of Normal Breast Milk Stools.—1. Direct smears from normal breast fed babies present a practically constant picture which is characterized by an almost complete dominance of the bifidus group. In this picture cocci and gram-negative organisms are indistinguishable or are present in very small numbers. This proportion of bacterial types may be changed by abnormal physiologic conditions.

2. A baby who has been on cow's milk formula for several days, although originally breast fed, may show, bacteriologically, the effects of this diet for as long as four weeks even after the continuous ingestion of breast milk. This is indicated in the direct smears from the

feces by a larger number of cocci and gram-negative bacilli than is typically characteristic of a normal breast milk stool.

3. If a cow's milk formula is used before the third day after birth and breast milk used thereafter the establishment of fecal types of bacteria follows the course of a normal nursling very closely.

4. From the study of anaerobic cultures it has been found that *B. bifidus* is also the dominant living type of organism in the feces of normal breast fed babies.

5. The proportion of types represented in the direct smears is closely paralleled by the proportion of types growing on anaerobic cultures.

6. Aerobic cultures from the feces of normal nurslings typically show a predominance of the colon-aerogenes groups. This may be lessened by abnormal physiologic conditions.

7. While the study of the fecal flora of infants by anaerobic culture seems to be of great importance, aerobic cultures should always be used as a check to determine the presence of aerobic pathogens or adventitious bacteria.

Bacteriology of Breast Milk.—1. The results obtained from the study of drawn breast milk used for supplementary bottle feedings are inconclusive since no definite relationship could be established between the types of fecal bacteria and the bacteria isolated from the milk. This was made more difficult because the babies had not had a monotonous diet which could be used as a check and because the majority of the organisms isolated from the milk were staphylococci and *B. coli* which may be isolated from any normal stool. This study did emphasize the fact that even a slight amount of handling may introduce certain types of bacteria into a bottle fed baby's feedings which a breast fed baby would not ordinarily ingest.

2. That a typical monotonous fecal flora follows the continuous ingestion of breast milk has been shown in the results obtained from the study of the stools of normal breast fed babies.

3. From the examination of the breast milk from the mothers here in the hospital it would seem that staphylococci may be ingested in all cases and that a "lactic acid" bacillus typical of *B. bifidus* may be frequently present in the milk as it comes from the breast.

4. An important question arises as to the identity of the "bifidus-like" bacillus which has been isolated from the breast milk and from the skin around the nipple. We do not hesitate to call this organism *B. bifidus*.

5. It is our belief that the bifidus organisms which are present in or on the mother's nipple are an important source of the bifidus organisms found in the nursling's intestines.

CLINICAL DEPARTMENT

A CASE OF ALKAPTONURIA IN AN INFANT *

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REPORT OF CASE

History.—June 10, 1921, a child was brought to me from one of the small towns of Oregon. The family history was negative. The child weighed 9 pounds at birth, and was breast-fed until 13 months of age. When examined, his age was 15 months; his weight 25 pounds. The child had had an uneventful infancy, and was a fine, happy, contented baby.

Examination.—The mother had noticed as soon as she had the care of the child following birth, that the diapers were stained dark brown by the urine. The skin of the diaper area was somewhat excoriated and stained brown. With this exception the physical examination was negative.

Urine.—A freshly voided specimen of urine was clear, amber colored and neutral in reaction. It contained no albumin or formed elements. It reduced Fehling's solution, but did not ferment. After standing a few minutes, the urine turned a dark brown color, and later became black.

When I was in the Great Ormond Street Hospital in 1908, Dr. Garrod demonstrated a similar case. After having seen a case of alkaptonuria there was no difficulty in recognizing the condition.

Alkaptonuria is the outward sign of a very rare anomaly of metabolism which is almost always congenital, and persists through life without any serious detriment to health. The peculiar properties of the urine are due to the excretion in it of an aromatic acid—homogentisic or hydroquinone-acetic acid—a product of the katabolism of tyrosin and phenylalanin. It is, in all probability, a product of normal metabolism which in normal individuals undergoes further change.

Alkapton urine seldom exhibits any abnormality of tint when passed, but darkens quickly on exposure to air, changing, in time, to brown and to black, resembling closely the changes seen in melanuric urines. However, the two conditions are distinguished readily by means of simple tests. When a dilute solution of ferric chlorid is added to alkapton urine, a deep blue color appears for a moment, and reappears after subsequent addition of the reagent, until oxidation of the homogentisic acid is completed. Unless the reagent is very dilute, oxidation occurs too rapidly, and the blue color is missed. The addition of an alkali causes very rapid darkening, with absorption of oxygen, and heat increases the rate of blackening.

As homogentisic acid is a powerful reducing agent, alkapton urine gives some of the reactions of glycosuria. Fehling's solution is reduced

* Received for publication, Nov. 5, 1921.

freely with the aid of heat, but the blackening effect of the alkaline reagent gives a peculiar appearance to the reaction. No black precipitate is obtained with Nylander's reagent, but the alkali therein causes conspicuous darkening. Alkapton urine does not undergo saccharin fermentation, nor does it rotate the plane of polarized light. An ammoniacal solution of silver nitrate is reduced rapidly even in the cold, a reaction which is made use of for the quantitative estimation of homogentisic acid.

The ingenuous theory has been advanced that alkaptonuria is the result of a chemical sport or alternative mode of metabolism. On a vegetable diet these subjects excrete less alkaptonic acids than on a meat diet. It is because alkaptonuria is so rare, only forty-five cases being reported up to 1920, rather than because its recognition presents any special difficulty, that it frequently is not recognized: Alkaptonic urine stains linen a dark brown color and often the condition is first discovered in this way.

Alkaptonuria is commoner in males than in females. Several cases are recorded in which the urine manifested all the characteristics of alkaptonuria on the day after the child was born; that is, as soon as any proteins reached the intestines, allowance being made for the oxidizing power of the tissues to destroy a certain amount of the homogentisic acid that is first formed. The first case of alkaptonuria in which homogentisic acid was found in the urine was that of a man 68 years of age, who had been alkaptonuric all his life (Baumann and Kraske). The sister of this man was 60 years of age when her case was investigated by Embden, and she also had been alkaptonuric from birth.

The cause of the abnormal color of alkapton urine was first investigated by Boedecker in 1859, who found in it a substance which had strong reducing powers and which darkened on exposure to air, especially after the addition of an alkali. To this substance he gave the name alkapton.

Alkaptonuria is almost always congenital and constant, though occasionally it develops after an illness. It occurs in families though not transmitted from parent to child, affecting several children of the same parents. Garrod quotes evidence to show that the children of first cousins are especially liable to alkaptonuria. In thirty-two known instances which were presumably congenital, nineteen occurred in seven families. One family contained four alkaptonurics, three others three, and the remaining three, two each.

It is never observed in mild form. If there is any homogentisic acid present in the urine, it is there in large amounts, from 4 to 5 gm. being excreted daily. When the error in metabolism is present at all, it is complete.

PROGRESS IN PEDIATRICS

REVIEW OF THE LITERATURE ON RESPIRATORY DISEASES FROM JANUARY, 1920, TO JUNE, 1921 *

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INTRODUCTORY

Bacteriology of Normal Throats.—Bloomfield¹ found by examinations of cultures made from a number of throat swabs from each of several healthy people that the organisms present, as revealed by this method, fell into two groups: (a) the true normal flora including non-hemolytic streptococci and gram-negative cocci, and (b) pathogenic or nonpathogenic organisms which are accidentally introduced and are present usually only a short time in a given individual. He felt that a true picture of the normal flora of the healthy throat was obtained only by making repeated cultures from the same individual.

Moss, Guthrie, and Marshall,² in a study of the experimental inoculation of healthy human throats with avirulent diphtheria bacilli, concluded that these organisms retain their characteristics despite long residence in the human throat or transfer from one human being to another, and further that they are devoid of pathogenic importance for man. Accordingly, they stated that the carrier of avirulent diphtheria bacilli does not constitute a menace to the health of the community.

Otteraaen³ found that hemolytic streptococci are frequent inhabitants of the throats of normal individuals as well as of persons suffering from acute infectious diseases. However, these streptococci are not virulent so far as indicated by the results of animal inoculation and phagocytosis experiments.

* Received for publication Dec. 22, 1921.

* From the Department of Pediatrics of Cornell University Medical College.

* This review was originally undertaken by Dr. Louis C. Schroeder, but after reviewing more than fifty articles, he was forced by pressure of other work to relinquish this study. He very generously contributed his notes to me for which I make grateful acknowledgment.

1. Bloomfield, A. L.: The Significance of the Bacteria Found in the Throats of Healthy People, Johns Hopkins Hosp. Bull. **32**:33 (Feb.) 1921.

2. Moss, W. L.; Guthrie, C. G., and Marshall, B. C.: Experimental Inoculation of Human Throats with Avirulent Diphtheria Bacilli, Johns Hopkins Hosp. Bull. **32**:37 (Feb.) 1921.

3. Otteraaen, A.: Hemolytic Streptococci in the Throat in Certain Acute Infectious Diseases, J. Infect. Dis. **26**:23 (Jan.) 1920.

In another article, Bloomfield⁴ showed that influenza bacilli quickly disappear from the normal mucous membranes of the mouth, nose and pharynx, after introduction of a pure culture on the tongue, on the nasal septum behind the vestibule, or into the nasopharynx. He suggested that the presence of the Pfeiffer bacillus in so-called healthy people may result from the persistence of a chronic focus in a sinus or in a bronchus, or from contact with an acutely infected person. With this view, Wollstein and Spence⁵ heartily agreed.

Incidence of Respiratory Disease.—Zahorsky⁶ noted that in his private practice the greatest actual number of cases of acute respiratory diseases sufficient to have the attention of a doctor occurred in infancy, with a decline in number each year to from 4 to 6 when there was a definite increase in the incidence, the time corresponding to the beginning of school life. After this period, the number of cases fell off rapidly. His figures, however, may, perhaps, be influenced by the nature of his practice which may be largely one of infants, so that he would be less apt to see respiratory disease in older children, even as he is quite unlikely to see it in adults.

COLDS AND ACUTE RESPIRATORY DISEASE IN GENERAL

Floyd⁷ divided "common colds" roughly into the following clinical types: (a) acute rhinitis; (b) acute pharyngitis, followed by rhinitis and laryngitis; (c) acute laryngitis, followed by tracheitis, bronchitis and pneumonia; (d) acute tracheitis, followed by bronchitis and laryngitis.

The acute rhinitis is characterized by sudden swelling of the nasal mucous membrane with a watery discharge, fullness in the head, and general malaise. The organism commonly found in the secretion belongs to the staphylococcus group, and somewhat less frequently the hemolytic streptococcus has appeared.

The acute pharyngitis is characterized by redness and swelling of the fauces and of the posterior wall of the pharynx, pain on swallowing, dry cough and fever. The infection may extend into the nose or larynx. Almost invariably the initial infection is produced by a member of the streptococcus group.

The types of cold beginning with laryngitis or tracheitis and followed by a rapid extension over the respiratory tract are closely related,

4. Bloomfield, A. L.: Fate of Influenza Bacilli Introduced into Upper Air Passages, Johns Hopkins Hosp. Bull. **31**:85 (March) 1920.

5. Wollstein, M., and Spence, R. C.: The Bacillus of Pfeiffer in Inflammations of the Respiratory Tract in Children, Am. J. Dis. Child. **19**:459 (June) 1920.

6. Zahorsky, J.: The Resistance to Acute Disease of the Respiratory Tract in Children, Am. J. Dis. Child. **21**:183 (Feb.) 1921.

7. Floyd, C.: The Common Cold in Relation to Certain Microorganisms and Its Treatment with Bacterial Vaccines, Boston M. & S. J. **182**:389, (April 15) 1920.

and are generally caused by the same microorganism. Aside from the local symptoms, the type is accompanied by considerable muscular pain, and the term "grippe" is commonly applied to it. The pneumococcus of Group IV, or occasionally of Groups I or II, is predominant. Occasionally, however, the hemolytic streptococcus has been the original invader. The early fall and winter colds are generally of the first types; the early and late spring colds are of the last two types.

Bloomfield⁸ defined the uncomplicated cold as "a mild disease manifesting itself by a constitutional reaction and by hyperemic phenomena of the upper air passages without local suppurative complications. The duration is brief and there is a tendency to leukopenia." On clinical grounds, he advanced the view that the common cold is an infectious disease analogous to influenza, featured by the frequent development of complications in the upper air passages, such as sinus infections, tracheitis and otitis. A review of the literature furnished him no convincing evidence that any known organism is the primary cause of the cold. The cultural studies in this report failed to show in uncomplicated cases any variation in the flora which enabled one to select any organism or group of organisms as the cause of colds. On the other hand, where clinical complications occurred, pathogenic organisms were definitely associated with them. He felt, therefore, that the primary cause of colds is probably an organism as yet unknown, and certainly not one of the usual pathogens, such as streptococci, pneumococci, *B. influenzae*, or staphylococci. But the primary cold, whatever its final cause, alters the mucous membranes in such a way as to allow secondary bacterial invasion and consequent frequent development of local complications. The cultures clearly indicated that such complications are due to a variety of bacteria, such as those just mentioned.

Wollstein and Spence⁵ noted that the influenza bacillus was not an inhabitant of the normal respiratory tract, but that at a time when an epidemic of influenza prevailed, it was present in more than 50 per cent. of all cases of inflammations of any part of the respiratory tract. At such times, this bacillus was found very commonly present in the sputum in cases of common colds with or without bronchitis, though these cases may be unaccompanied by general or systemic symptoms and have no relation to influenza.

After an elaborate study, Mudd, Grant, and Goldman⁹ recognized the following causes of acute inflammations of the pharynx, tonsils, and nose:

1. The filtrable virus of Kruse and Foster, inducing apparently a clinical entity, a type of acute coryza. According to the experiments

8. Bloomfield, A. L.: Variations in the Bacterial Flora of the Upper Air Passages During the Course of Common Colds, Johns Hopkins Hosp. Bull. 32:12 (April) 1921.

9. Mudd, S.; Grant, S. B., and Goldman, A.: The Etiology of Acute Inflammations of the Nose, Pharynx and Tonsils, J. Lab. & Clin. M. 6:175 (Jan.), 253 (Feb.), 322 (March) 1921.

of its discoverers, this is of relatively high virulence, and may cause infection practically independently of the action of exciting factors.

2. Various bacteria, including the pneumococcus, streptococci, *B. rhinitis*, *B. diphtheriae*, Friedländer's bacillus, *B. influenzae*, and probably also *M. catarrhalis*, *B. septus*, *M. paratetragenus*, *Staphylococcus aureus*, and possibly others, seem to be capable of inducing infection of variable extent, duration and symptomatology.

3. Protein sensitization, the basis of vasomotor rhinitis and of true bronchial asthma, the underlying cause also of a relatively infrequent subgroup of acute recurrent "colds."

4. Various systemic diseases, drugs, mechanical and chemical irritants, chronic nasal affections and reflex neuroses.

These authors believe that one factor by which resistance to bacterial infection may be lowered is excessive chilling, probably not by lowering the body temperature but through causing a vasoconstriction and local ischemia in the mucous membranes of the nasopharynx.

Paunz¹⁰ commented on the frequent discovery in child cadavers of inflammatory and suppurative processes in the sinuses communicating with the nose. In older children an acute infectious disease is generally responsible for the sinusitis but in infants even coryza or tonsillitis may develop this complication. In six of his eleven cases, the sinusitis followed coryza, including one 6 weeks old infant.

Prophylaxis.—Preventive measures against acute respiratory diseases require the intelligent cooperation of every individual in a community, according to Overton.¹¹ The attitude of each person must be to report sickness rather than to conceal it, to suspect suspicious signs rather than to ignore them, to impose some degree of self isolation rather than to mingle closely with others, and to observe personal hygiene rather than to assert an excessive degree of personal liberty and independence. The preventive measures against acute respiratory diseases are the same as those against other communicable diseases and include the discovery of the cases in their early stages, their isolation to some degree and the careful and strict disposal of the excretions of their noses and mouths.

Sobel¹² especially urged keeping young children well away from others with respiratory infections, and considered the home the place where most emphasis was needed on this subject. He stressed the proper care of the young children to increase their resistance to such infections, and noted that wet and cold both lower this resistance markedly. He urged the proper treatment of mild infections, such as

10. Paunz, M.: Complications of Sinusitis in Children, *Jahrb. f. Kinderh.*, **93**:313, 1920; *Abstr. J. A. M. A.* **76**:147 (Jan. 8) 1921.

11. Overton, F.: Some Epidemiological Points Regarding Acute Respiratory Disease, *Am. J. Pub. Health* **10**:431 (May) 1920.

12. Sobel, J.: The Prevention of Respiratory Diseases in Infancy and Early Childhood, *Med. Rec.* **97**:817 (May 15) 1920.

colds and bronchitis, to prevent the more severe infections such as pneumonia.

Evidence as to the desirability of keeping children and others with colds away from schools, "movies," and other crowded places is found in the bacteriologic study made by Huddleson and Hull¹³ on the air of an amusement hall. During the height of an epidemic of bad colds, the air of the amusement hall filled with soldiers was so badly contaminated that an average of eighty-two organisms fell on blood agar plates exposed only one minute, while eight days later, after the epidemic had subsided, an average of only sixteen colonies developed on the plates exposed under the same conditions but for a period of ten minutes. In picking colonies indiscriminately from the incubated plates used when the epidemic was at its height, four pneumococci of type IV were found as well as many hemolytic and nonhemolytic streptococci, numerous staphylococci, and gram-negative and gram-positive diplococci. In contrast to this, the types found on the plates used when the epidemic had subsided, were chiefly molds and staphylococci, no pneumococci being found. Sixteen per cent. of the total number were streptococci which showed partial but not complete hemolysis (Alpha type).

Lynch¹⁴ argued for boiling dishes, table silver, mess-kits, and the like to prevent the spread of respiratory diseases, especially in connection with community eating such as army camps, restaurants, etc., and in homes where one case of respiratory disease exists. His work was based on field and laboratory study of many army units of which some boiled their mess-kits and some did not.

Kellogg and MacMillan's¹⁵ experiments showed quite definitely that face masks have a very limited value in checking epidemics of respiratory diseases. Some of their conclusions have been reached by other authors but few have done as carefully controlled experiments. Their final conclusion is that masks have not been demonstrated to have a degree of efficiency that would warrant their compulsory application for the checking of epidemics.

A great deal of work has been done by a number of groups of workers in the study of the prophylactic use of various vaccines against colds, influenza and other acute respiratory infections, and a review of much of the work will be found under the heading of influenza. Park,¹⁶ in reviewing the results of the studies of his co-workers, noted

13. Huddleson, I. F., and Hull, T. G.: Bacteria of the Air in an Amusement Hall, *Am. J. Pub. Health* **10**:583 (July) 1920.

14. Lynch, C.: Prevention of Respiratory Diseases, *Med. Rec.* **98**:799 (Nov. 13) 1920.

15. Kellogg, W. H., and MacMillan, G.: An Experimental Study of the Efficacy of Gauze Face Masks, *Am. J. Pub. Health* **10**:34 (Jan.) 1920.

16. Park, W. H.; Williams, A. W., and Krumwiede, C.: Microbial Studies on Acute Respiratory Infection with Especial Consideration of Immunological Types, *J. Immunol.* **6**:1 (Jan.) 1921.

that the percentage of colds was as great among the vaccinated as among the unvaccinated, and similar results were obtained by other investigators. On the other hand, Floyd⁷ stated that "the production of an active immunity through the use of appropriate bacterial vaccines promises to be of value prophylactically in the control of infections of the upper respiratory tract."

Treatment.—In an article on the treatment of "colds" and "grippe," Fantus¹⁷ recognized chilling as an exciting factor, and therefore did not favor sweating, as a rule, unless great care is taken to avoid damp clothing with subsequent chilling. While "hardening" should be used in prophylaxis, "coddling" is the rule of safety for catarrhal fevers, and he urged stay in bed for three days after the return of normal temperature, and complete stay in bed during the period of fever.

With the possible exception of alkalies, he considered the use of medicines merely symptomatic. Expectoration should be helped by saline expectorants and by fluid. He advocated sodium citrate, from 1 to 2 gm. in lemonade or orangeade every two hours.

McGuigan¹⁸ noted that menthol and peppermint lessen the surface viscosity of the mucous exudates in catarrhal conditions and act similarly on the membranes producing the exudates, thereby relieving the obstruction of nasal breathing in "colds." For this effect the menthol must be in solution or in a condition in which volatility can act. He noted also that similarly the viscosity of a liquid is increased about 2 per cent. for each degree the temperature is lowered. So where the expulsion of mucus is desired, warm moist respired air will greatly aid the expulsion, while cold air will increase the difficulty.

INFLUENZA

A great deal of work has been done in various parts of the country by groups of investigators on the pathogenesis of epidemic influenza. In stating the purpose of the studies of their own group of workers, Park, Williams and Krumwiede¹⁸ defined the problems which attracted the attention of most of the investigators. These problems were four in number:

1. A study of the microorganisms of the upper respiratory tract in "health," in "common colds" and in "influenza." This investigation should include the diligent search for an epidemic microbial strain in influenza cases. Both filtrable and unfiltrable microbes were to be considered.

2. A continuation of the studies of hemoglobinophilic bacilli (group of the influenza bacillus), for the purpose of establishing the relation-

17. Fantus, B.: Therapy of Catarrhal Fevers, J. A. M. A. **75**:1694 (Dec. 18) 1920.

18. McGuigan, H.: Menthol and Peppermint in Acute Catarrhal Conditions of the Respiratory Tract, J. A. M. A. **76**:303 (Jan. 29) 1921.

ship of the influenza bacillus to both pandemic and sporadic cases of influenza.

3. A study of the permanence of type characteristics of influenza bacilli in persons after recovery from respiratory infections. It was considered of the utmost importance to establish as accurately as possible the stability of types.

4. A study of the incidence of common colds, influenza, and pneumonia, following the controlled use of a vaccine made up of different types of bacilli claimed to be the cause of acute respiratory diseases.

Park summarized the results of the studies that were made by himself and his associates. Of the different groups of microorganisms isolated by their procedure, all had the peculiarity that each group was an assemblage of many types. This was equally true for the pneumococcus, the influenza bacillus, the green-producing streptococcus, and the hemolytic streptococcus. They "obtained no evidence of the existence of a common filtrable organism."

In a study of case incidence alone, they found that some groups may be ruled out as being implicated in the epidemic; such as staphylococci, gram-negative cocci, and hemolytic streptococci. They thought more work could be done on pneumococci, green streptococci, indifferent streptococci, and some of the minority groups with a high case incidence.

Coca and Kelley¹⁹ noted that investigators had various opinions as to the bacteriologic causation of epidemic influenza.

1. There are those who think that the influenza bacillus of Pfeiffer is the cause of the disease.

2. Others believe that influenza is caused by a filtrable virus.

3. Some found a "gram-positive streptococcus" or a diplococcus.

Influenza Bacillus.—The influenza bacillus of Pfeiffer has been the subject of much investigation. During the first quarter of 1920, the period of the latest epidemic of influenza in New York City, Wollstein and Spence⁵ studied 1,000 sputum cultures, 294 of which were from adults, nurses and doctors, the rest from children who were hospital patients or dispensary cases. They found the influenza bacillus in 85 per cent. of all the cases of rhinitis and bronchitis that were severe enough to produce systemic reactions, and in 53 per cent. of the cases of ordinary colds, but in only 11 per cent. of their controls. They concluded that the bacillus of Pfeiffer is not specific to influenza in that it is present in from 50 to 80 per cent. of cases of mild respiratory infections clinically not related to influenza. It seemed to grow on any

19. Coca, A. F., and Kelley, M. F.: Studies on Acute Respiratory Infections. VI. A Serological Study of the Bacillus of Pfeiffer, *J. Immunol.* **6**:87 (Jan.) 1921.

portion of the respiratory tract which was congested, but proof that it was ever the primary cause of this congestion was lacking. That the local and general symptoms may be influenced by its presence, however, they believe to be true.

Blake and Cecil²⁰ found that in monkeys the influenza bacillus can act as a primary incitant of respiratory infection without the assistance of a preceding or concomitant contributing cause. By intra-tracheal injection of this organism, they produced in normal monkeys an acute infection of the upper respiratory tract, complicated by acute sinusitis, tracheobronchitis, hemorrhagic edema of the lungs, bronchiolitis and bronchopneumonia, in fact, a disease apparently essentially identical with influenza with respect to its clinical course, symptoms and complications. They felt that the etiologic relationship of the influenza bacillus to acute sinusitis, tracheobronchitis, bronchiolitis and bronchopneumonia was established, and also that it was reasonable to infer from the results of their experiments that this microorganism was the specific cause of influenza. However, they did not feel that this last conclusion was entirely permissible since it is impossible to determine whether the respiratory disease produced in monkeys with the influenza bacillus is identical with influenza or merely similar to it.

Rosenow²¹ admitted the possibility that the influenza bacillus may play a rôle in the production of symptoms and lesions in influenza, citing this work of Blake and Cecil and believing they were enabled to produce in monkeys influenza-like symptoms and lesions by means of influenza bacilli which had undergone changes and acquired high virulence through repeated monkey passages.

Cecil and Steffen²² found that virulent influenza bacilli, when injected into the nose and throat of healthy volunteers, may excite in them an acute respiratory disease similar in many respects to influenza but falling short of the typical clinical picture. In such cases influenza bacilli, biologically identical with those inoculated, may be recovered from the discharges as long as symptoms persist and often for some

20. Blake, F. G., and Cecil, R. L.: The Production of an Acute Respiratory Disease in Monkeys by Inoculation with Bacillus Influenza. A Preliminary Report, *J. A. M. A.* **74**:170 (Jan. 17) 1920; The Production in Monkeys of an Acute Respiratory Disease Resembling Influenza by Inoculation with Bacillus Influenzae, *J. Exper. M.* **32**:691 (Dec.) 1920; Studies on Experimental Pneumonia: The Pathology of Experimental Influenza and of Bacillus Influenzae Pneumonia in Monkeys, **32**:719 (Dec.) 1920.

Editorial: The Cause of Influenza, *J. A. M. A.* **76**:523 (Feb. 19) 1921.

21. Rosenow, E. C.: Studies in Influenza and Pneumonia: IX. Changes in the Green-Producing Streptococcus Induced by Successive Animal Passage and Their Significance in Epidemic Influenza, *J. Infect. Dis.* **26**:567 (June) 1920.

22. Cecil, R. L., and Steffen, G. L.: Acute Respiratory Infection in Man Following Inoculation with Virulent Bacillus Influenzae, *J. Infect. Dis.* **28**:201 (March) 1921.

time thereafter. This they thought was in sharp contrast to the work of Bloomfield who found that strains of this bacillus isolated from healthy mouths disappeared rapidly after injection into the healthy nose and throat.

Filtrates of influenza bacillus cultures when similarly injected into two healthy volunteers produced neither local nor constitutional reaction. On the other hand, they found that the inoculation of healthy volunteers with virulent hemolytic streptococci may in some cases induce an acute follicular tonsillitis with fever and leukocytosis. But a virulent pneumococcus of Type IV was injected into the nose and throat of two healthy volunteers with impunity. Accordingly, they conclude that it is possible the pneumococci and certain others of the bacteria that are associated with coryza and sore throats, invade the tissue only after some depression in the local and general resistance of the host. The capacity of all these bacteria to act as secondary invaders cannot be questioned, but the experiments reported in this paper indicate that virulent influenza bacilli possess a peculiar power of attacking healthy mucous membrane and of exciting a respiratory infection quite similar in some of its clinical manifestations to spontaneous influenza.

After reporting a case of infection following accidental inoculation with the Pfeiffer bacillus, Park and Cooper²³ concluded that freshly isolated Pfeiffer bacilli are capable of causing infection when transferred in great numbers to susceptible mucous membranes. Strains recovered from infected persons at varying intervals after the accidental inoculation revealed agglutinative characteristics identical with those of the strains which had caused the infection. The varying periods cover the time from shortly after infection to convalescence. This they considered strong evidence that a strain responsible for an infection would reveal identical characteristics during infection and convalescence in the epidemic cases due to its invasion. However, if the epidemic of influenza was due to the Pfeiffer bacillus, they would expect the dominant strains to have similar type characteristics. The fact that just the opposite condition exists they consider strong proof against the primary etiologic importance of the Pfeiffer bacillus in epidemic influenza.

After a study of complement fixation in influenza with *Bacillus influenzae* antigens, Cooke²⁴ found that complement fixation antibodies can be demonstrated in the serum of a considerable number of older

23. Park, W. H., and Cooper, G.: Studies on Acute Respiratory Infections. V. Accidental Inoculation of Influenza Bacilli on the Mucous Membranes of Healthy Persons with Development of Infection in at Least One. Persistence of Type Characteristics of the Bacilli, *J. Immunol.* **6**:81 (Jan.) 1921.

24. Cooke, J. V.: Complement Fixation in Influenza with *B. Influenzae* Antigens, **27**:476 (Dec.) 1920.

children and adults convalescent from influenza, by the use of such antigens, but that these antibodies are much less constantly found in children from 1 to 5 years of age. With the serums tested, however, he could detect no definite antigenic relationship between the sixteen strains of the influenza bacillus. He thought that his results indicate that the bacillus of Pfeiffer is pathogenic and infects many, if not all, patients with influenza. He felt, however, that the complement fixation test could not furnish sufficient evidence to justify the conclusion that this microorganism is the sole etiologic agent in influenza.

Coca and Kelley¹⁹ repeated Park's argument that the most characteristic feature of influenza, namely, its pandemic occurrence, which distinguishes it from all other infectious diseases, requires the assumption of a single etiologic factor in its causation. For this it is not sufficient in order to prove the casual relationship of Pfeiffer's bacillus to influenza that an obligative hemophilic pathogenic bacillus be found in all or nearly all cases of influenza. It is necessary in addition to show with the aid of reliable biologic reactions such as that of agglutination that the cultures obtained from influenza patients that are known not to have been in contact with one another, are identical. Coca and Kelley went on to report that confirming previous work of Valentine and Cooper, a study of eighteen cultures of the bacillus of Pfeiffer isolated from cases of influenza in different localities and at different times, revealed identities in the cultures only when a probability of personal contact existed. From this they decided that on the basis of Park's argument these findings admit of only one conclusion with regard to Pfeiffer's bacillus, namely, that microorganism is not the cause of the disease.

Rosenow²⁵ and his co-workers believed that many epidemics of typical influenza occur that are not due to the influenza bacillus, since this microorganism was found in their studies only occasionally in comparison to certain other organisms. And whereas after the intratracheal injection of influenza sputum or lung exudate, he noted²⁶ the invasion of certain other organisms, invasion by the influenza bacillus did not occur in a single experiment.

Uthelm²⁷ found that during uncomplicated influenza, the body does not always form antibodies against its own infecting strain of the influenza bacillus. Of thirty strains isolated from patients with

25. Rosenow, E. C.: Studies in Influenza and Pneumonia: V. Observations on the Bacteriology and Certain Clinical Features of Influenza and Influenzal Pneumonia, *J. Infect. Dis.* **26**:469 (June) 1920.

26. Rosenow, E. C.: Studies in Influenza and Pneumonia: VII. A Study of the Effects Following the Injection of Bacteria Found in Influenza in Normal Throats, in Simple Nasopharyngitis, and in Lobar Pneumonia, *J. Infect. Dis.* **26**:504 (June) 1920.

27. Uthelm, K.: Agglutination in Influenza, *J. Infect. Dis.* **27**:460 (Nov.) 1920.

influenza, eleven, or 36 per cent., gave agglutination with the patient's serum. Seven of these instances occurred in cases of uncomplicated influenza and four in cases of influenzal pneumonia. Of the remaining nineteen negative cases, ten were cases of pneumonia. Of the thirty strains, only one was agglutinated by heterologous serum.

Small and Dickson²⁸ concluded that the hemophilic microorganisms (*B. influenzae*) can be grouped by immunologic methods, and they demonstrated four groups into two of which 70 per cent. of the organisms studied fell.

After an elaborate study of agglutination and absorption tests on thirty-six strains of influenza bacilli with twenty-seven immune serums, Bell²⁹ concluded that the influenza bacillus represents a heterogeneous group of organisms, though identical strains do occur. The morphology alone was unreliable as a means of dividing this group of organisms into subgroups. He found that a person may carry in the throat three different strains of this organism at the same time. By his serum test methods, he could make no differentiation between the organisms isolated from normal healthy throats within two months preceding the epidemic and those isolated from the throats of influenza patients.

Povitsky and Denny³⁰ also studied the grouping of influenza bacilli and found that in most cases, the organisms obtained from a number of colonies fished in a given case proved to be of one type, or at least, one type greatly predominated. In a minority of instances, the colonies from the same case were not of the same type, as proved by agglutination absorption tests using homologous and heterologous serums. However, in carriers, or when the infection was mild, more than one type of the influenza bacillus was apt to be found in the same case. On the other hand, in several convalescent carriers, tests were made during periods of from three weeks to three months, resulting in the finding of the original type of the influenza bacillus in all but one case, and in another case tests made a year apart proved the original type still present.

So, according to Wade and Manalang,³¹ the problem of the causative agent of influenza and especially that of the importance of the Pfeiffer bacillus, until recently generally believed to be the infecting organism in this disease, seems still far from solution. They referred to many

28. Small, J. C., and Dickson, G. K.: Grouping of *Bacillus Influenzae* by Specific Agglutination, *J. Infect. Dis.* **26**:230 (March) 1920.

29. Bell, H. H.: Relation of Different Strains of Influenza Bacilli as Shown by Cross Agglutination and Absorption Tests, *J. Infect. Dis.* **27**:464 (Nov.) 1920.

30. Povitsky, O. R., and Denny, H. T.: Studies on Acute Respiratory Infections: IV. Further Studies on Grouping of Influenza Bacilli with Special Reference to Permanence of Type in the Carrier, *J. Immunol.* **6**:65 (Jan.) 1921.

31. Wade, H. W., and Manalang, C.: Fungous Development of Growth Forms of *B. Influenzae*, *J. Exper. M.* **31**:95 (Jan.) 1920.

investigators who have cultured minute filtrable organisms and stated that if influenza is a virus disease, as now seems likely, it may be that the influenza bacillus has no primary relation to it. However, this cannot yet be asserted as a fact, for gradually the possibility is gaining recognition that familiar organisms of supposedly fixed morphology may assume a filtrable stage. Their observations then went on to show that the Pfeiffer organism is unstable and the familiar bacillus is but a simple form of an organism capable of complex development.

A Filtrable Virus.—In May, 1920, Olitsky and Gates²² made a preliminary report of the finding of a filtrable substance in the pharyngeal secretions in the early hours of uncomplicated epidemic influenza, which substance induced a clinical and pathologic condition in rabbits similar to influenza in man. They believed they were dealing with the actual transmission of a multiplying agent rather than with a passive transference of any original active substance.

The manner in which the bacteria of ordinary species, such as the pneumococcus, the Pfeiffer bacillus, *Streptococcus viridans*, and others are encountered during the course of the transmission experiments and during the experimental reproduction described justifies the opinion that these microorganisms are secondary in effect. The essential effects are produced by a substance wholly unrelated to these bacteria.

Following the above report, Olitsky and Gates³³ published a series of articles further describing their investigations. In the first one, they cited the criteria used in the selection of their cases of pure influenza as

abrupt onset with chilliness, fever, prostration, headache, and muscular pains especially in the back and limbs. Among the early symptoms were flush and suffusion of the face, injection of the conjunctivae, soreness of the throat, and harsh unproductive cough. In the early stages, no physical signs were detected in the chest; gastro-intestinal symptoms were inconspicuous, and disturbances referable to other internal organs were not complained of or detected by physical examination. These symptoms, although striking, were rarely such as could be measured accurately. However, there was one sign that had a quantitative value, namely the leukocytic picture. Uncomplicated influenza shows a pronounced leukopenia affecting the absolute number of mononuclear cells, chiefly the lymphocytic variety. This is persistent and even resists at times secondary infectious processes, eg., pneumonia, in which leukocytosis is the rule. . . . The symptoms and effects endured for from one to three days, when convalescence initiated by a lytic fall of temperature set in, and recovery promptly followed.

32. Olitsky, P. K., and Gates, F. L.: Experimental Study of the Nasopharyngeal Secretions from Influenza Patients, *J. A. M. A.* **74**:1497, (May 29) 1920.

33. Olitsky, P. K., and Gates, F. L.: Experimental Studies of the Nasopharyngeal Secretions from Influenza Patients: I. Transmission Experiments with Nasopharyngeal Washings, *J. Exper. M.* **33**:125 (Feb.) 1921. II. Filterability and Resistance to Glycerol, **33**:361 (March) 1921. III. Studies of the Concurrent Infections, **33**:373 (March) 1921. IV. Anaerobic Cultivation, **33**:713 (June) 1921. V. Bacterium Pneumosintes and Concurrent Infections, **34**:1 (July) 1921.

At this point it is interesting to note that Rosenow³⁴ concluded after a study of blood counts in men and in animals that the leukopenia in influenzal infection in man may be due to peculiar properties of the bacteria which are now generally regarded as secondary invaders, and not to an unknown virus. Moreover, according to his findings, a persistent marked leukopenia or an increasing leukopenia in influenza predisposes to influenzal pneumonia, and in the latter indicates a bad prognosis.

To return to the work of Olitsky and Gates, they continued to say that with the aforementioned clinical picture as their guide of the pure influenza, they detected, by methods they described, an active substance in the nasopharyngeal washings of five patients in early stages of epidemic influenza during 1918-1919, and in two more in 1920. This active substance was not detected in twelve cases of the same disease in which the onset of obvious symptoms occurred more than thirty-six hours before washing of the nasopharynx was carried out, nor was it found in the secretions of fourteen individuals free from the syndrome of influenza either during the epidemics or the interval between them. They noted that the active agent as it exists in the nasopharyngeal secretions in man and in the lungs of rabbits injected with human secretions, passes through Berkefeld V and N candles. With this active agent, whether in filtered or unfiltered material, they induced in rabbits a clinical and pathologic condition affecting mainly the blood and pulmonary structures, which condition could be maintained and carried through at least fifteen successive animals. The similarity that existed between the effects produced in rabbits in the blood ("changes in the absolute and differential white blood cell count") and the lungs ("certain hemorrhagic, edematous and emphysematous changes") and those occurring in man in epidemic influenza provided these authors with a basis for further investigation as to the inciting agent of epidemic influenza.

Olitsky and Gates next announced³⁵ that using the anaerobic Smith-Noguchi technic, they had cultivated from the filtered nasopharyngeal washings from early cases of uncomplicated epidemic influenza and from the lung tissues of experimental animals, a minute bacilloid body from 0.15 to 0.3 microns in length, of constant cultural characteristics and capable of indefinite propagation on artificial mediums. They stated that this organism grows only under strictly anaerobic conditions, passes Berkefeld V and N filters, and withstands

34. Rosenow, E. C.: Studies in Influenza and Pneumonia: VI. The Leukocytic Reaction in Influenza and Influenzal Pneumonia, *J. Infec. Dis.* **26**:492 (June) 1920.

35. Olitsky, P. K., and Gates, F. L.: Studies of the Nasopharyngeal Secretions from Influenzal Patients: Preliminary Report on Cultivation Experiments, *J. A. M. A.* **76**:640 (March 5) 1921.

the action of sterile 50 per cent. glycerol for a period of months. They gave it the name of *Bacterium pneumosintes* (from πνεύμων, lung, and δίντης, injurer or devastator) since a striking feature of its effect in rabbits is to diminish the resistance of the lungs to the action of ordinary bacteria. This bacterium appeared to the authors to be identical with the active agent previously reported and to be the source of the reactions which occur in experimental animals, rabbits and guinea-pigs, as a result of the intratracheal injection of nasopharyngeal washings obtained during the early hours of uncomplicated epidemic influenza in man. They deferred decision, however, as to the precise relation which the species described bears to epidemic influenza in man, until further experience was obtained.

In two previous papers, Olitsky and Gates³³ stated that in no instance did death occur in the experimental rabbits as a result of the uncomplicated effects of the influenzal agent alone. When death occurred in any of the inoculated animals, concurrent infection of the lungs by ordinary bacteria was present. In fact, their experiments showed that the lungs of animals infected with the *Bacterium pneumosintes* are less resistant than normal lungs to infection with ordinary bacteria, the pneumococcus Type IV, atypical Type 2 streptococci, and hemoglobinophilic bacilli, being most commonly met. They believed that a similarity exists between the conditions under which concurrent infections arose in the inoculated rabbits and those which seem to favor the occurrence of concurrent infections during epidemic influenza in man. They further believed that their observations furnished additional proof of the identity of *Bacterium pneumosintes* and the active agent derived from the nasopharyngeal secretions of patients in the early hours of epidemic influenza.

It is to be hoped that in future papers, Olitsky and Gates will give further information as to the identity and pathogenicity of their interesting bacterium. In the meanwhile, Loewe and Zeman³⁶ have already reported the cultivation of a filterable organism from the nasopharyngeal washings in influenza, and they stated that their organism does not appear to differ from that recovered by Olitsky and Gates. M. W. Hall³⁷ has reported that it is possible by the injection into the circulation of bacteriologically sterile filtrates of sputum from early cases of influenza to produce in animals lesions of a uniform type uncomplicated by the presence of demonstrable bacteria but quite comparable to the so-called primary lesions of influenza reported by many. He believed that his results seem to give support to the theory

36. Loewe, L., and Zeman, F. D.: Cultivation of a Filtrable Organism from the Nasopharyngeal Washings in Influenza, J. A. M. A. **76**:986 (April 9) 1921.

37. Hall, M. W.: A Study of the Lesions Produced by Filtrates of Influenza Sputum, Arch. Int. Med. **26**:612 (Nov.) 1920.

of a filtrable agent as the primary cause of influenza. The active agent concerned is markedly resistant to heat, and probably is mainly intracellular in character, he thought. He further noted that, according to the early reports, the work of Olitsky and Gates in many ways parallels his, with apparently harmonious results.

The theory that influenza is caused by a filterable virus has not been accepted without exception. Williams, Nevin and Gurley,³⁸ of Park's associates, reported an unusually comprehensive procedure for collecting and handling material, and yet stated "the negative results obtained by our procedure for demonstrating filtrable microbes, we consider an indication that the positive results already reported do not bear as wide an application as their sponsors infer."

Branham and I. C. Hall³⁹ reported that in attempting to cultivate filtrable viruses from the nasopharyngeal secretions in colds and influenza, no bodies were found in the cultures which could not also be found in those from normal persons, but they recognized that negative experiments limited to the attempted cultivation of a filtrable virus and including no attempts to reproduce the disease in animals, do not offer conclusive evidence that such a virus is not involved. Nor did they work on cases of influenza during the earliest stages of the disease. In a separate paper, I. C. Hall⁴⁰ stated that the probability of obligate anaerobes developing in the respiratory tract seems slight in view of the excessive air supply, and that his findings indicate that such infections occurred, if at all, only infrequently in the cases of respiratory disease presented for examination during the winter and spring of 1920.

Other Micro-Organisms in Influenza.—Tunncliffe⁴¹ noted that from influenza and its complications during the onset and at the height of the 1918-1919 epidemic, various investigators had isolated peculiar green-producing cocci with the characteristics of both a pneumococcus and a streptococcus. These green-producing cocci are oftener lanceolate than round, generally possess a capsule, and produce large moist green colonies on blood-agar plates. She herself succeeded in isolating this

38. Williams, A. W.; Nevin, M., and Gurley, C. R.: Studies on Acute Respiratory Infections: I. Methods of Demonstrating Microorganisms, Including "Filterable Viruses" from the Upper Respiratory Tract in "Health," in "Common Colds," and in "Influenza" with the Object of Discovering "Common Strains," *J. Immunol.* **6**:5 (Jan.) 1921.

39. Branham, S. E., and Hall, I. C.: Influenza Studies: III. Attempts to Cultivate Filtrable Viruses from Cases of Influenza and Common Colds, *J. Infect. Dis.* **28**:143 (Feb.) 1921.

40. Hall, I. C.: Influenza Studies: II. A Search for Obligate Anaerobes in Respiratory Infections, an Anaerobic Micrococcus, *J. Infect. Dis.* **28**:127 (Feb.) 1921.

41. Tunncliffe, R.: Observations on Green Producing Cocci of Influenza, *J. Infect. Dis.* **26**:405 (May) 1920.

coccus from the edematous brain in influenzal broncho-pneumonia, usually in pure culture, but in no instance did she cultivate the Pfeiffer bacillus from the brain. From her serologic experiments she decided that these green-producing influenzal cocci form a group the members of which are closely related immunologically.

Rosenow and his coworkers²⁵ also studied this green-producing streptococcus, finding it in a large series of cases of influenza and influenzal pneumonia throughout four different epidemic waves, more constantly and in larger numbers than any other organisms associated with the disease. Rosenow noted²¹ that the virulency and mortality in animals increased for one or two successive intratracheal injections of this microorganism, and on further animal passage diminished. And after a study of the four epidemic waves as they occurred in Rochester, Minnesota, he found that a similar rise and fall in severity of symptoms, mortality and character of lung lesions occurred as the epidemic waves appeared and disappeared. Accordingly he thought that (1) the change in the type of the disease early and late in the epidemics, (2) the rise and fall in mortality rate in the same epidemic, and in the virulency of different epidemics, and (3) the lesser tendency to leukopenia late in epidemic waves, may all be due, in the main, to changes in virulency and other properties of the green-producing streptococcus isolated so constantly in influenzal infections. He further noted⁴² that whereas these peculiar green-producing streptococci are immunologically quite homogenous at the outset of an epidemic, the strains tend to become more heterogenous after cultivation on artificial mediums, and after repeated animal passages as well as late in influenza and influenzal pneumonia.

Rosenow also studied the four main types of bacteria isolated in this disease as to their invasive powers following intratracheal injection of influenzal sputum. Invasion by the green-producing streptococcus group (including pneumococci), occurred in most instances even when not the predominating organism in the material injected. In some instances, invasion by hemolytic streptococci occurred, but usually only when they were present alone or in predominating numbers. Invasion by staphylococci occurred even more rarely and only when in predominating numbers; and invasion by the influenza bacillus following the injection of sputum and lung exudate did not occur in a single experiment.

Recapitulating, Rosenow wrote,²⁶

Through a painstaking study of the infecting powers of the streptococcus in influenza and influenzal pneumonia throughout several epidemic waves, it

42. Rosenow, E. C.: Studies in Influenza and Pneumonia: X. The Immunologic Properties of the Green Producing Streptococci from Influenza, *J. Infect. Dis.* 26:597 (June) 1920.

has been possible to reproduce in animals by various methods of injection, but particularly by intratracheal injection, the picture of influenza as seen in man. The symptoms both of influenza and influenzal pneumonia have been grossly simulated in these animals as far as possible. Likewise the gross and microscopic changes which have come to be regarded as quite characteristic of influenzal infection have been reproduced. The same varied picture that often supervenes in the later stages of influenzal pneumonia in man such as leukocytosis as evidence of pleural involvement and pleural infection, becomes manifest and the varied pathologic picture in the lung of patients who died late has been noted in guinea-pigs injected intratracheally with these strains. The tendency to involvement of the female generative organs with a high mortality in pregnancy and a high incidence of abortion, of lesions of the heart, abscess in the rectus muscle, and interstitial emphysema, have been noted in the experimental animal quite as they occur in man.

Cooper, Mishulow and Blanc⁴³ studied the pneumococcus in connection with common colds and influenza-like cases, and found no single variety of this organism dominant in the inflammatory conditions studied. They found no data to indicate that the pneumococcus is the primary etiologic agent in the contagious types of these inflammations. Bakwin⁴⁴ found pneumococci in seven out of thirty-five antemortem blood cultures in cases of influenzal pneumonia. The remainder were sterile, with the exception of one, which showed a meningococcus.

Influenzal Pneumonia: Pathology.—Bakwin⁴⁴ made a study of the findings of 106 necropsies on cases of influenzal pneumonia in the American army in France. He noted that the disease was general, affecting not merely the lungs but all the organs, being accompanied by jaundice, cloudy swelling of the parenchymatous organs and heart muscle, and hemorrhages into the pericardium, renal pelvis and other viscera. Changes in the rectus muscle were observed in one-third of the cases, and sphenoid sinusitis was found in twenty out of twenty-two cases examined. Empyema was rare, occurring in less than 4 per cent. of the cases.

Warwick⁴⁵ reported the case of an infant which was apparently normal at birth but at 3 days of age developed a temperature of 105 F. and died the following day. The necropsy revealed a peculiar hemorrhagic process involving the greater part of both lungs, a pathologic picture which was practically identical with the so-called "hemorrhagic broncho-pneumonia" which was seen so frequently in patients dying

43. Cooper, G. M.; Mishulow, L., and Blanc, N. E.: Studies on Acute Respiratory Infections: II. A Study of the Serological Relationships of Pneumonia from the Upper Respiratory Tract with Special Reference to Common Colds and Influenzal Conditions, *J. Immunol.* **6**:25 (Jan.) 1921.

44. Bakwin, H.: Gross Pathology of Influenzal Pneumonia in France, *Am. J. M. Sc.* **159**:435 (March) 1920.

45. Warwick, M.: Necropsy Findings in New-Born Infants, *Am. J. Dis. Child.* **21**:488 (May) 1921.

of influenza. Since this case occurred early after the outbreak of the 1918 influenza epidemic, it was probably an instance of this disease in a new-born infant, an uncommonly rare occurrence.

Influenzal Types, Complications and Sequels.—Stengel⁴⁶ clinically classified cases as of influenzal pneumonia or lobar pneumonia by a consideration of the history, the character and extent of the physical signs, and by the leukocytic count.

Cases regarded as influenzal pneumonia have invariably shown diffuse physical signs, commonly bilateral, and always much less clearly marked than in lobar pneumonia, and the leukocytic count has usually been below 10,000, while the differential count has commonly shown a relative deficiency in neutrophils, or at least no increase. The development of the signs of pneumonia is somewhat gradual and irregular, following a clear picture of ordinary influenza. On the other hand, the cases regarded as lobar pneumonia have had sudden onset of symptoms of pneumonia and a rapid development of physical signs with clearly marked lobar consolidation. The leukocytic count was above 12,000 and the proportion of neutrophils marked (from 80 to 90 per cent.).

The experiments made as a basis of his studies suggested to Rosenow⁴⁷ that there is a true gastro-intestinal type of influenza, and that green-producing streptococci, similar to those isolated from the respiratory tract, are the chief cause. He went on to say, however, that it is not to be concluded that all symptoms in influenza referable to the gastro-intestinal tract are due to localization of bacteria in its mucous membrane. In certain of his experiments it was shown that the symptoms and findings in influenza are due, in part, to an anaphylactoid reaction; the severe vomiting and diarrhea noted at the outset of some cases may be an expression of this mechanism.

Amesse⁴⁸ wrote in a recent article that he believed that influenza in its acute epidemic form is merely latent at present, yet at the same time the disease is present in occasional dual relation with everyday disease. The observation of such unusual complications of chickenpox, measles, etc., as meningitis and meningismus, complications which occur in influenza also, has led him to believe that influenza may assume different varieties, and that the "unusual features noted in the study of more common disorders justify the impression that we are frequently dealing with a double infection"—presumably of the common disorder and some variety of influenza.

46. Stengel, A.: On the Use of Serum and Blood of Convalescent Patients in the Treatment of Lobar Pneumonia and Influenzal Pneumonia, *M. Clinics N. America* **4**:937 (Jan.) 1921.

47. Rosenow, E. C.: Studies in Influenza and Pneumonia: VIII. Experiments on the Etiology of Gastro-Intestinal Influenza, *J. Infect. Dis.* **26**:557 (June) 1920.

48. Amesse, J. W.: Unusual Complications and Sequellae in the Acute Infections of Childhood following the Influenza Epidemic, *Colorado Med.* **18**: 56 (March) 1921.

Meyer and Lucke⁴⁹ reported seven cases of subcutaneous emphysema following influenza in soldiers. They believed that it arose chiefly as a result of the escape of air from ulcerated or eroded bronchi and its subsequent passage along peribronchial or perivascular channels into the mediastinum. In at least two of their cases, they found marked ulcerative bronchitis and subcutaneous emphysema, both located on the left side.

Fishberg⁵⁰ observed that in many patients attacked by acute epidemic influenza, certain sequels are left in the respiratory tract after the acute infection has run its course. He enumerated subacute rhinopharyngitis, general bronchitis, localized bronchitis resembling tuberculosis and very difficult to differentiate from it, bronchiectasis and pulmonary abscess.

Epidemiology.—The epidemic of respiratory diseases of January, 1920, differed from the epidemic of 1918 in that the total number of persons affected was less, the proportion of acute rapidly fatal cases was smaller, and the period of the epidemic was shorter.⁵¹ In an elaborate statistical study of the 1918 epidemic of influenza in Connecticut, Winslow and Rogers⁵² noted that the epidemic cost the state about 7,700 lives and was by far the most serious sanitary calamity from which Connecticut has ever suffered. Apparently the case rate in affected communities varied from 200 to 400 cases per thousand of population, and the fatality rate between two and four deaths per hundred cases. "The rapid spread of the disease throughout the state and the fact that quarantine completely protected isolated groups of individuals (so long as the quarantine was rigidly maintained) indicates clearly that it was transmitted by human contact, perhaps supplemented in certain cases by the use of infected food and utensils."

Treatment.—Sterling⁵³ noted that quinized malarial patients in hospital in Italy were practically immune to the epidemic raging around them. Accordingly he made a plea for the use of 15 grains of quinin hydrobromid on retiring, as a prophylactic measure against epidemic influenza.

49. Meyer, J., and Lucke, B.: Subcutaneous Emphysema; A. Complication of Influenza Pneumonia. Report of Seven Cases, *Am. J. M. Sc.* **159**:417 (March) 1920.

50. Fishberg, M.: Pulmonary Sequels of Influenza, *Am. J. M. Sc.* **161**:365 (March) 1921.

51. Editorial: Influenza of 1918 and 1920, *J. A. M. A.* **74**:736 (March 13) 1920.

52. Winslow, C-E. A., and Rogers, J. F.: Statistics from the 1918 Epidemic of Influenza in Connecticut, with a Consideration of the Factors which Influenced the Prevalence of this Disease in Various Communities, *J. Infect. Dis.* **26**: 185 (March) 1920.

53. Sterling, A.: Quinine as a Prophylactic and Specific for Influenza, *Pennsylvania M. J.* **23**:719 (Sept.) 1920.

Holt⁵⁴ analyzed the statistics of the Visiting Nurse Service of the Henry Street Settlement during the influenza epidemic of October and November, 1918, where 162 nurses visited and reported on 10,655 cases of influenza and pneumonia under the care of physicians in the patients' homes. One thousand, six hundred and twenty-five cases are left out of his final tabulation, the cases having been mild and not requiring subsequent visits, or terminated before the arrival of the nurse, or for some other similar reason. Of the remaining 8,740 cases, the mortality was as follows:

Type of case, influenza; number treated, 6,243; deaths, 115; mortality per cent., 1.6. Pneumonia: number treated, 2,497; deaths, 485; mortality per cent., 19.4. Totals: number treated, 8,740; deaths, 600; mortality per cent., 6.9.

Holt added that cases of simple influenza and of influenzal pneumonia are accordingly best treated in the patients' homes or when separated as much as possible. His figures also indicated that the frequency and the severity of the complications are much increased in proportion as patients are crowded together.

At the Mare Island Naval Station, the final development of the treatment of influenza which gave the best results, has been set down by Neilson⁵⁵ as follows: (a.) Absolute rest in bed. (b.) Thorough and constant alkalization either by mouth or by Murphy drip. (c.) Sodium salicylate intravenously, only in cases not complicated by pneumonia and then only when pain, restlessness, and high temperature, evidenced severe toxemia. (d.) Magnesium sulphate intravenously in pneumonia cases showing bad general condition, high temperature, and falling white count. (e.) Blood transfusion from immune donors (citrate method with whole blood) in pneumonia cases showing cyanosis, rise in temperature (either when first seen or after failure to react permanently to magnesium sulphate intravenously), and a falling white count. (f.) Stimulation used more sparingly, and only when indicated for special purpose or in selected case. Whisky, digitalin, or camphor, used as stimulant. (g.) Sodium iodid in a simple cough mixture to relieve a troublesome dry cough. (h.) Magnesium sulphate by mouth for catharsis. (i.) Carbohydrate diet.

The death rate at this station among those receiving the more specific forms of treatment was lower than the death rate given in any statistics that have come under the observation of the writer, from other points at which the disease was of an equally severe type.

54. Holt, L. E.: Home versus Hospital Care of Cases of Influenza, *Med. Rec.* **97**:731 (May 1) 1920.

55. Neilson, J. L.: Treatment of Influenza, *U. S. Nav. M. Bull.* **15**:259 (April) 1921.

Hogan⁵⁶ gave details of the preparation and administration of the magnesium sulphate-calcium chlorid mixture spoken of by Neilson, and stated that there had been only 16 per cent. of deaths in fifty severe cases of influenzal pneumonia treated with this mixture against a mortality of 40 per cent. in similar cases treated symptomatically only.

Rosenow⁵⁷ used an immune serum prepared from one strain of the green-producing streptococcus, and treated twelve patients with influenzal pneumonia, of whom eleven were critically ill at the time of serum treatment. Five recovered. In all cases in which specific agglutination was obtained, marked improvement followed the injection of the serum, and in no case were good effects noted at a time when agglutination tests were negative. Of the seven deaths, two were caused by hemolytic streptococci, two by a strain of green-producing streptococcus immunologically different from that of the serum, and three of the patients were moribund at the time of treatment.

Stengel⁴⁶ treated nine patients all seriously ill with influenzal pneumonia, by the intravenous injection of from 30 to 70 c.c. of blood serum from patients recently convalescent from the disease, and all recovered, but a tenth patient, moribund on admission, failed to survive.

Immunity.—Jordan and Sharp⁵⁸ made a statistical study of several thousand men at the Great Lakes Naval Station and at Camp Grant, to find out which men, attacked in the 1920 epidemic, had been attacked in the 1918-1919 epidemic and which had not. Their results indicate that no marked immunity to influenza exists from twelve to fifteen months after a previous attack.

The use of vaccines as a means of producing artificial immunity against influenza has been studied by a number of observers. McCoy⁵⁹ decided that the Pfeiffer bacillus alone or in combination had no practical uses. Park¹⁹ remarked that the evidence of immunologic response to the vaccines by his co-workers was apparent only in the lessened incidence of pneumonia. The percentage of colds was as great among the vaccinated as among the unvaccinated. The pneumonia incidence was much less. The greater multiplicity of types of microbes believed to be capable of exciting common colds over those usually exciting pneumonia is possibly the explanation of the apparent uselessness of

56. Hogan, J. J.: Intravenous Use of Magnesium Sulphate and Calcium Chloride in Severe Pneumonia Complicating Influenza, U. S. Nav. M. Bull. **15**:277 (April) 1921.

57. Rosenow, E. C.: Studies in Influenza and Pneumonia: XI. Therapeutic Effects of a Monovalent Antistreptococcus Serum in Influenza and Influenzal Pneumonia, J. Infect. Dis. **26**:614 (June) 1920.

58. Jordan, E. O., and Sharp, W. B.: Influenza Studies: I. Immunity in Influenza, J. Infect. Dis. **26**:463 (May) 1920.

59. McCoy, G. W.: Application of Vaccines in Public Health Work, Am. J. Pub. Health **10**:666 (Aug.) 1920.

the vaccines employed in this series in preventing minor respiratory infections while apparently affording considerable protection against pneumonia. The vaccine that Von Sholly and Park⁶⁰ used in this work contained 2,000 million per c.c. each of pneumococcus Types I and II, and 1,000 million each of pneumococcus Type III, *Streptococcus hemolyticus*, *Streptococcus viridans*, and the influenza bacillus.

Similar results to those of Von Sholly and Park were obtained by Jordan and Sharp⁶¹ who stated that rhinitis and bronchitis developed with about equal frequency in the vaccinated and unvaccinated groups. Their figures suggested a favorable conclusion regarding some slight prophylactic value for pneumonia, but that any considerable degree of protection against influenza was conferred by the vaccine, seemed unlikely.

On the other hand, Gay⁶² noted a rising enthusiasm among writers as to the value of mixed vaccines containing various strains of influenza bacilli, pneumococci, streptococci and staphylococci, not only to diminish the incidence of influenza in a community but also for decreasing the pneumonic complications of the disease.

(To be continued)

60. Von Sholly, A. I., and Park, W. H.: Studies on Acute Respiratory Infections: VII. Report on the Prophylactic Vaccination of 1,536 Persons Against Acute Respiratory Infections, 1919-1920, J. Immunol. **6**:103 (Jan.) 1921.

61. Jordan, E. O., and Sharp, W. B.: Influenza Studies: IV. Effect of Vaccination against Influenza and Some Other Respiratory Infections, J. Infect. Dis. **28**:356 (April) 1921.

62. Gay, F. P.: The Use of Vaccines in the Prevention and Treatment of Influenza and Its Sequels, J. A. M. A. **76**:244 (Jan. 22) 1921.

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INDICATIONS FOR THE REMOVAL OF THE SPLEEN IN INFANTS AND CHILDREN *

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Hemolytic jaundice, Banti's disease, Gaucher's disease and von Jaksch's anemia, are four names given to pathologic processes for the relief or cure of which removal of the spleen may be the only treatment.

Hemolytic jaundice, in the yellowness of the skin and sclera, presents an outward and visible sign which gives obvious aid in the determination of a diagnosis.

Banti's disease and Gaucher's disease have no distinguishing symptoms and physical signs by which they can be identified clearly. It is impossible in the early stages, and difficult even in the later stages, to give a name to the pathologic process representing these diseases, and it is just in the early stage of Banti's or Gaucher's disease that splenectomy is of greatest value.

Von Jaksch's disease is at present sub judice, being regarded by some as not a distinct entity. Figures 1, 2 and 3 are the microphotographs of a spleen of Banti's disease and Figures 4 and 5 of a spleen of Von Jaksch's disease. A comparison of these two sets of pictures would justify the statement that they might be two stages of the same pathologic process.

In view of the difficulty of giving a name (Banti's disease; Gaucher's disease) to certain symptom complexes in which anemia and a large spleen are the prominent manifestations, and for which splenectomy may be the only proper treatment, it is necessary to have certain criteria for the removal of the spleen. These criteria will be brought out in the analysis of the two cases of Banti's disease and one of Gaucher's disease which are reported in this paper. They were treated by splenectomy.

An attempt has been made to collect the reports of all previous splenectomies in children under 14 years of age. Table 1 contains this information. No doubt some reports have been missed in the search. Information about splenectomies not recorded in this table would be appreciated, as a complete record is desired. The table represents a total of fifty-one splenectomies which are distributed as follows: von Jaksch's disease, 5; splenic anemia and Banti's disease, 20; Gaucher's

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TABLE 1.—SUMMARY OF SPLENECTOMIES DONE ON CHILDREN UNDER 14 YEARS OF AGE

Diagnosis	Author	Age and Sex	Spleen	Blood Examination	Result	Remarks
1. von Jaksch's anemia	Pool, F. H.; Ann. Surg. 61 : 349, 1915	8 mos. Male	6.5 cm. below costal margin; $10 \times 7 \times 4$ cm.; Wt., $3\frac{1}{2}$ oz.; malpighian bodies few, small and indistinct; myeloidization of pulp	Before splenectomy: R.B.C. 1,400,000 to 2,400,000; Hb. 30-45%; E. 2%; L. 49%; W.B.C. 17,000-54,000; P. 35%; T. 3%; L.M. 1%; Myel. 50%; nucleated reds 6-66 per 100 W.B.C.; megakaryoblasts. After: 4,000,000; Hb. 85%; nucleated reds 131 per 100 W.B.C.	Died of bronchopneumonia 2 mos. after discharge	
2. von Jaksch's anemia	Stillman, R. G.; Am. J. M. Sc. 153 : 218, 1917	9 yrs. Female	15 cm. below costal margin; Wt., 1,420 gm.; vascular increase connective tissue; follicles small, indistinct; sinuses filled with large undifferentiated mononuclear cells; pulp contains myelocytes; monoblasts, R.B.C.	Before splenectomy: R.B.C. 2,400,000; Hb. 25%; W.B.C. 15,000; P. 40%; nucleated red cells. After 23 mos.: R.B.C. 4,600,000; Hb. 65%; W.B.C. 19,200; P. 31%; nucleated reds	6 yrs. after operation: Hb. about 60%; much improved (Stillman's personal communication)	Spleen large since 2 yrs. of age; else regarded by Krumbhaar as possible hemolytic jaundice
3. von Jaksch's anemia	Ibid	18 mos. Female	Edge 6.5 cm. below costal margin; Wt., 227 gm.; $14\frac{1}{2} \times 9\frac{1}{2} \times 3\frac{1}{2}$ cm.; malpighian bodies about normal in size, numerous; trabecula indistinct; pulp more cellular than normal, contains many monoblasts, R.B.C. and myelocytes	Before splenectomy: R.B.C. 2,700,000; Hb. 43%; W.B.C. 12,000; P. 47%; 12 nucleated cells to 100 W.B.C.; polychromatosis anisocytosis, polychromatophilic. After 8 months: R.B.C. 5,700,000; Hb. 67%; W.B.C. 21,900; P. 38%	3 yrs. after operation perfectly well; blood picture practically same as after 8 months	Premature 7 mos.; Wassermann negative
4. von Jaksch's anemia	Thursfield, H. D., Gow. A. E.; Splenectomy and splenectomy, St. Bartholomew's Hosp. Rep. 50 : 59, 1914	17 mos. Male	Spleen to symphysis and midline; Wt., 500 gm.; thickening of trabecula; pulp infiltrated in the cells resembling myelocytes	Before splenectomy: R.B.C. 467,000; Hb. 40%; W.B.C. 37,800; normoblasts and megakaryoblasts. After: 9% yrs.; R.B.C. 5,000,000; W.B.C. 6,200; morphologically normal	Cured; 3 yrs. after splenectomy, healthy	Case originally reported by Wolf, H.; Berl. klin. Wchnschr. 63 : 1565, 1906
5. von Jaksch's anemia	French, H., and Turner, P.; Case of Splenic Anemia treated by Splenectomy, Proc. Roy. Soc. Med. 7 : Clin. Sec. 77 , 1913-14	5 yrs. Male	Spleen enlarged at 6 months before operation; Wt., 18 oz.; 7×5 inches	Before splenectomy: R.B.C. 1,900,000; Hb. 20%; W.B.C. 21,000. After: Hb. 85%	17 mos. after operation is rosy-cheeked normal boy, attending school, apparently cured	Wassermann positive
1. Splenic anemia (Banti's disease)	Anesae, J. W.; Splenic Anemia in Children, Colorado Med. 17 : 12, 1920	6 yrs.	Weight about 2 lbs.; $17 \times 7 \times 7$	Before splenectomy: R.B.C. 1,900,000; Hb. 30%; W.B.C. 5,300. After 3 mos.: R.B.C. 5,200,000; Hb. 80%; W.B.C. 13,000; P. 47%; S.L. 38%	1½ yrs. after splenectomy: patient goes to school and enters into general games; gained 20 lbs.; eats well and sleeps well	Anemia since 3 yrs. old
2. Banti's disease	Gaston, J. M.; Two Splenectomies, Their Lessons, Internat. Clin., ser. 30, 1 : 194, 1920	14 yrs. Male	Enlarged to navel; Wt., 3 lbs.	Before splenectomy: Hb. 80%.....	8 mos. after operation: has gained in weight and was in good health	
3. Splenic anemia (Banti's disease)	Fowler, R. S.; Splenectomy for Splenic Anemia, N. Y. State J. M. 14 : 435, 1914	14 mos. Female	No history of enlarged spleen; Wt., 150 gm.; splenic pulp firmer than normal; microscopically typical of splenic anemia; distinct increase of fibrous tissue	Before splenectomy: R.B.C. 3,316,000; Hb. 50%; W.B.C. 30,000; P. 40%; L.M. 12%; S.M. 89%; many normoblasts; occasional megakaryoblasts; anisocytosis; achromia. After 1 mo.: R.B.C. 3,430,000; Hb. 65%; W.B.C. 15,000; P. 20%; S.M. 78%; T. 2%; polychromes; anisocytosis; monoblasts; megakaryoblasts	1 month after operation much improved	
4. Splenic anemia	Fowler; Ibid	5½ yrs. Sex ?	Anemia more marked than in above case	After leaving hospital child died of recurrence of intestinal hemorrhages	No further details in the report

5. Splenic anemia (Banti's)	Giffin, H. Z.: Splenectomy for Splenic Anemia in Childhood. <i>Ann. Surg.</i> 62: 679, 1915	2½ yrs. Female	No history of enlargement; Wt., 100 gm.; moderately diffuse fibrosis; hypertrophy of reticula-endothelium of the sinuses	Before splenectomy: R.B.C. 2,010,000; Hb. 20%; W.B.C. 4,000; P. 22%; S.L. 50%; E. 2.3%; L.L. 12.3%; Bas. 2.3; Neut. myelocytes 3%; 1 normoblast to 300 cells; R.B.C. showed anisocytosis and moderate polychromatophilia. After 3 days: Hb. 27%; W.B.C. 14,600; P. 71.3%; normoblasts 76 to 300 W.B.C.	Not stated	In same article Sherren mentions a splenectomy in a boy 14 yrs. with advanced cirrhosis of the liver; death 48 hrs. after operation; no further details
6. Banti's disease	Sherren, James: Surgical Treatment of Certain Diseases by Splenectomy. <i>Ann. Surg.</i> 68: 379, 1918	12 yrs. Male	Spleen enlarged; Wt., 18 oz.; fibrosis of reticulum of pulp; hemorrhage and slight deposit of iron frequent in and around adventitia of vessels close to malpighian bodies	Before splenectomy: R.B.C. 4,300,000; Hb. 75%; W.B.C. 2,300; P. 54%; E. 2%; S.L. 20%; L.L. 30%; L. hyalin cells 4%. After 1 mo. R.B.C. 4,800,000; Hb. 80%; W.B.C. 5,000; P. 75%; E. 2.5%; S.L. 5%; L.L. 8.5%; L. hyalin cells 8.5%; T.O. 3%	4 yrs. after operation in perfect health	
7. Splenic anemia (Banti's)	Knott, v. B.: Splenic anemia in a 5 Years' Old Boy, J. A. M. A. 52: 963, 1909	5 yrs. Male	Enlargement of spleen noticed same year; Wt., 500 gm.; 17.1×9×4 cm.; increase of connective tissue throughout	Before splenectomy: R.B.C. 1,762,000; Hb. 32%; W.B.C. 5,880; P. 78%; L.L. 4%; S.L. 17%; myelocytes 1%. After 1 mo.: R.B.C. 4,240,000; Hb. 82%; W.B.C. 4,250; S.L. 28%; myelocytes 1%	Improvement soon after operation marked	
8. Splenic anemia (Banti's)	Hall, F. de Havilland, and Spencer, W. S.: Splenectomy for Splenic Anemia. <i>Proc. Roy. Soc. Med.</i> 2: Clin. Sec. 238, 1909	8½ yrs. Female	No history of enlargement of spleen; Wt., 2½ lbs.; spleen showed nothing abnormal except enlargement of vessels with blood	Before splenectomy: R.B.C. 4,060,000; Hb. 65%; W.B.C. 1,200; P. 28%; L. 75%. After 1½ mos.: R.B.C. 4,550,000; Hb. 62%; W.B.C. 12,000; P. 40%; L. 15%	2 mos. after operation patient reports good appetite, though showing slight anemia	
9. Banti's disease	D'Espine, A.: La Maladie de Banti chez l'Enfant. <i>Rev. med. d. l. Suisse</i> 33: 336, 1913	15½ mos. Female	Wt., 201 gm.; 11×7×3.5; spleen showed hyperplasia with diffuse fibrosis and excess of the myeloid elements	Before splenectomy: R.B.C. 3,700,000; Hb. 45%; W.B.C. 13,640; P. 52%; L. 33%; T. 4%; L.M. 8%; E. 1%; normoblasts few. After 1 mo.: R.B.C. 2,660,000; Hb. 50%; W.B.C. 33,720; P. 31%; L. 43%; T. 7%; L.M. 18%; E. 0.5%	Child improved after operation, but died 5 weeks after of bronchopneumonia	
10. Splenic anemia	Sargent, P.: Case of Splenic Anemia Treated by Splenectomy. <i>Proc. Roy. Soc. Med.</i> 7: Clin. Sec. 76, 1913-14	10 yrs. Female	Edge of spleen palpable on admission	Before splenectomy: R.B.C. 4,300,000; Hb. 40%; W.B.C. 2,000; P. 63%; S.L. 33%; L.L. 5%; fair number of normoblasts; moderate polkilocytosis. After 13 mos.: R.B.C. normal; no normoblasts; P. 35%; S.L. 58.5%; L.L. 1.5%	One year after operation fairly good health	November, 1912, abdomen began to enlarge
11. Splenic anemia (Banti's)	Hoffman, G.: Case of Splenic Anemia Treated by Splenectomy. <i>Proc. Roy. Soc. Med.</i> 7: Clin. Sec. 78, 1913-14	12 yrs. Female	Spleen projected 2½ in. below costal margin, 21 mos. before operation; perisplenitis and cirrhosis	Before splenectomy: R.B.C. 4,400,000; Hb. 90%; W.B.C. 3,600. After 3 yrs. and 10 mos.: R.B.C. 5,475,000; Hb. 100%	In good health; no hemorrhages 3 yrs. 10 mos. after operation	R.B.C. had previously been as low as 2,500,000
12. Banti's disease	Grützner: Beitrag zur Lehre vom Morbus Banti. <i>Beitr. z. Klin. Chir.</i> 85: 131, 1913	10 yrs. Female	No history of enlarged spleen; Wt., 450 gm.; 19×12×4.5 cm.; capsule and trabecula made up of thick bluish fibers; similar fibers throughout entire reticulum; lymphocytes in pulp diminished	Before splenectomy: R.B.C. 2,400,000; Hb. 20%; W.B.C. 2,700; P. 64%; L. 32.5%; E.O. 5%; normoblasts and transitional 3%; polkilocytosis; slight anisocytosis. After 4 weeks: R.B.C. 3,500,000; Hb. 80%; W.B.C. normal	Immediate improvement after operation; no late results stated	
13. Splenic anemia (Banti's)	Hutchinson, J.: Excision of the Spleen for Splenic Anemia. <i>Proc. Roy. Soc. Med.</i> 6: Surg. Sec. 236, 1912-13	11 yrs. Male	Spleen enlarged and tender 4 yrs. previously; spleen showed firm hypertrophy of the whole organ without signs of inflammation	Before splenectomy, 1 mo.: R.B.C. 2,100,000; Hb. 30%; W.B.C. 3,800; P. 63.5%; S.L. 23.5%. After 2 mos.: R.B.C. 3,000,000; Hb. 65%; W.B.C. 9,400	One year after operation in excellent health	

TABLE 1.—SUMMARY OF SPLENECTOMIES DONE ON CHILDREN UNDER 14 YEARS OF AGE—(Continued)

Diagnosis	Author	Age and Sex	Spleen	Blood Examination	Result	Remarks
14. Splenic anemia (Banti's)	Sutherland, G. A., and Burghard, F. F.: Treatment of Splenic Anemia by Splenectomy, <i>Lancet</i> 2: 1819, 1910	12 yrs. Female	Spleen not enlarged before operation; Wt., 2 lbs.; hyperplasia of all tissues	Before splenectomy: R.B.C. 2,500,000; Hb. 40%; W.B.C. (3 mos. before) 9,800. After 3 days: R.B.C. 4,700,000; Hb. 70%. After 4 yrs.: R.B.C. 3,600,000; Hb. 78%; W.B.C. 6,400	4 yrs. after operation in good health; in service as a nurse maid	
15. Splenic anemia (Banti's)	Ibid	6 yrs. Female	Pain in splenic region 2 mos. before admission; spleen enlarged	Before splenectomy: R.B.C. 1,870,000; Hb. 30%; W.B.C. 2,400; normoblasts about 600 per cm. After 17 days: R.B.C. 5,200,000; Hb. 65%; W.B.C. 3,400	7 weeks after operation improvement continuing	
16. Banti's disease	Luce, H.: Zur Pathologie der Bantischen Krankheit, <i>Med. Klin</i> 6: 535, 1910	6 yrs. Female	Spleen noted large 3 mos. before operation; Wt., 240 gm.; pulp filled with R.B.C.; lymphatic elements reduced; fibrous tissue reduced; malpighian bodies more numerous and larger	Before splenectomy: R.B.C. 1,400,000; Hb. 20%; W.B.C. 11,980. After 1 yr.: R.B.C. 4,100,000; Hb. 65%; W.B.C. 8,600; P. 45.9%; L. 45.3%; L.M. and Tl. 3%; E 7.5%	One year after operation in excellent health	
17. Splenic anemia	Giffin, H. Z.: Private communication	2½ yrs.	Chronic splenitis	Before splenectomy, 1 day: R.B.C. 2.1; Hb. 18%; W.B.C. 5,800. After 1 mo.: R.B.C. 2.32; Hb. 19%; W.B.C. 14,400	Symptoms noted 1 mo. before operation. Urine exam. 1 da. previous to operation: Amt. 200; Sp. Gr. 1.004; React. alk.; Alb. 2
18. Splenic anemia	Ibid	8 yrs.	Chronic splenitis (fairly marked fibrosis); multiple small hemorrhagic areas scattered throughout spleen	Before splenectomy, 4 days: R.B.C. 4.53; Hb. 75%; W.B.C. 2,800. 28 days after: R.B.C. 4.53; Hb. 68%; W.B.C. 15,000	Symptoms noted 3 mos. before operation. Urine exam. 14 da. previous to operation: Amt. 400; Sp. Gr. 1.028; React. acid; negative
19. Splenic anemia	Ibid	2½ yrs.	Chronic splenitis; marked fibrosis; multiple small hemorrhages throughout	Before splenectomy, 26 days: R.B.C. 2.57; Hb. 38%; W.B.C. 5,400. After 5 days: R.B.C. 4.41; Hb. 72%; W.B.C. 21,800	First hemorrhage 16 days before operation; tumor 6 mos. Urine exam. 25 da. previous to operation: Amt. 300; Sp. Grav. 1.023; React. acid; Alb. 1; Pus 1
20. Splenic anemia	Ibid	8 yrs.	Chronic splenitis	Before splenectomy, 5 days: R.B.C. 2.82; Hb. 37%; W.B.C. 8,300. After 26 days: R.B.C. 2.62; Hb. 32%; W.B.C. 12,000	Died 2½ months after operation	Symptoms noted 2 mos. before operation. Urine exam. 1 mo. previous to operation: Amt. 800; Sp. Gr. 1.014; React. acid; Alb. 2
1. Tuberculosis....	Ibid	10 yrs.	Chronic splenitis with localized areas of milary tuberculosis	Before splenectomy, 23 days: R.B.C. 4.40; Hb. 35%; W.B.C. 7,900. After 13 days: R.B.C. 4.04; Hb. 40%; W.B.C. 18,000	Symptoms 2 yrs. before operation. Urine exam. 23 da. previous to operation: Amt. 350; Sp. Gr. 1.019; React. acid; Alb. 0; pus negative

1. Septic splenomegaly	Ibid	10 yrs.	Reddish spleen with numerous malpighian bodies; slight increase fibrous tissue; spleen is color of splenomyelogenous leukemia	Before splenectomy, 5 days: R.B.C. 4,14; Hb. 61%; W.B.C. 6,800. After 15 days: R.B.C. 3,42; Hb. 45%; W.B.C. 14,200	Died 7 mos. after operation	Symptoms for 8 wks. 2 trans. pre-op. Urine exam. 6 da. previous to operation: Amt. 400; Sp. Gr. 1.027; React. acid; Alb. 1; pus negative
1. Hemolytic jaundice (congenital)	Nobel: Berl. Klin. Wehnschr. 51: 1150, 1243, 1914; report taken from Elliott and Kanavel: Splenectomy and Hemolytic Icterus, Surg., Gyn. & Obst. 21: 32, 1915	Child Male	Enlarged spleen noted.....	Before splenectomy: R.B.C. 800,000 (half nucleated); Hb. 15%; W.B.C. 100,000. After: R.B.C. 3,600,000; Hb. 47%; W.B.C. 10,000	Rapid recovery after operation; jaundice gone	Jaundice and urobilinuria noted 1 mo. before operation; this reference not verified in original article; fragility R.B.C. increased
2. Hemolytic jaundice (congenital)	Ibid	8 yrs. Male	3 fingers below costal margin	Before splenectomy: R.B.C. 2,600,000; Hb. 46%. After 10 days: R.B.C. increased; Hb. 71%	Jaundice gone after 10 days	Jaundiced soon after birth; yellow since then; urobilinuria; fragility of R.B.C. increased
3. Hemolytic jaundice (probably congenital)	Römer: München. med. Wehnschr. 1914. No. 9, 50; also Wien. Med. Wehnschr. 64: 1029, 1914; taken from Elliott and Kanavel's table (see No. 1)	11 yrs	Blood entirely normal after operation	Jaundice disappeared; blood normal; cured; (no date given)	Urobilin in both urine and stools before operation
4. Hemolytic jaundice (type not indicated)	Pollitzer, H.: Fall von Splenomegalia haemolytica, Wien. klin. Wehnschr. 26: 952, 1913	13 yrs. Female	Spleen noted large at 2 yrs.; Wt., 650 gm.	Slight anemia, excess of leukocytes; polychromasia normoblasts (no counts given)	Jaundice disappeared after operation	Urobilin in both urine and stools before operation
5. Hemolytic jaundice (type not indicated)	Graf, P.: Zur Chirurg. Therapie des haemolyt. Icterus, Deutsch. Ztschr. f. Chir. 130: 462, 1914	13 yrs. Female	Before splenectomy: R.B.C. 2,600,000; Hb. 40%; W.B.C. 11,600. After 10 mos.: R.B.C. 6,900,000; Hb. 80%; W.B.C. 11,400	10 mos. after operation patient was strong and able to work; countenance somewhat yellow; liver still large	Urine contained urobilinogen none after operation
6. Hemolytic jaundice (type not indicated)	Schneider, J. P.: Two Splenectomized Cases. Minn. Med. 21: 210, 1919	13 yrs. Female	Before splenectomy: R.B.C. 2,904,000; Hb. 49%; W.B.C. 4,500; P. 60%; L.L. 15%; S.L. 24%; E. 5%; anisocytosis marked. After 15 days: R.B.C. 3,975,000; Hb. 58%; W.B.C. 12,000	Well 6 mos. after operation	Abdominal distention noted for 2 years past; urine; urobilin and urobilinogen in large amounts before operation; none 9 days after operation
7. Hemolytic jaundice (type not indicated)	Giffin, H. Z.: Hemolytic Jaundice, a Review of 17 Cases, Surg., Gyn. & Obst. 25: 152, 1917	9 yrs. Male	Wt., 1,370 gm.	Before splenectomy: R.B.C. 1,340,000; Hb. 24%; W.B.C. 15,300; P. 50%; S.L. 29%; L.L. 4%; E. 2.3%; Baso. 57% Megal. 3%; normoblasts 57 to 300 W.B.C. After 18 days: R.B.C. 2,260,000; Hb. 38%; W.B.C. 12,600; P. 64%; S.L. 16.3%; L.L. 10.7%; E. 6.7%; Baso. 1.7%	1 yr. and 3 mos. after operation in excellent health	
8. Hemolytic jaundice	Whipple, T. R. C.: Splenomegalia Hemolytic Jaundice, Lancet 2: 1194, 1914	6 yrs. Female	Enlarged 3 mos. before operation	Before splenectomy: R.B.C. 994,000; W.B.C. 13,180. After 3 mos. and day before death: R.B.C. 5,500,000; Hb. 70%; W.B.C. 23,400; Index 63	Died 3 mos. after operation	Jaundice at birth; lasted 6 wks.; good health until 3 mos. before operation; urine before op. contained bile pigment, also before death day before death jaundice and epistaxis

TABLE 1.—SUMMARY OF SPLENECTOMIES DONE ON CHILDREN UNDER 14 YEARS OF AGE—(Continued)

Diagnosis	Author	Age and Sex	Spleen	Blood Examination	Result	Remarks
9. Hemolytic jaundice	Box, C. R.: Case of Excision of Spleen for Congenital Family Cholelithiasis. <i>Proc. Roy. Soc. Med.</i> , 6: Dis. Child. Sec. 8, 1913	12 yrs. Female	Enlargement of spleen since infancy; Wt., 300 gm.; moderate perisplenitis; splenic tissue had undergone fibrosis; sinuses dilated	Before splenectomy: R.B.C. 3,337,000; Hb. 65%; W.B.C. 10,640; P. 59%; S.L. 4%; L.L. 3.75%; large hyaline cells 3.6%; E. 2.25%. After 5 wks.: R.B.C. 3,808,750; Hb. 75%; W.B.C. 21,280; P. 60.25%; S.L. 25.25%; L.L. 3.75%; E. 13.5%; large hyaline cells 0%; mast cells 1.25%. Before splenectomy: R.B.C. 2,550,000; Hb. 25%; W.B.C. 7,800; differential normal; anisocytosis; polkioleucosis; polychromatophilic; few normoblasts. After 3 mos.: R.B.C. 4,890,000; Hb. 75%; W.B.C. 12,000; P. 62%; L.M. 5%; megalocytes 6%; no nucleated R.B.C.	5 wks. after operation much improved; 5 days later died; uræmic convulsions. P.M.: abscesses in splenic stump and nephritis	Jaundice for 6 wks. after birth
10. Hemolytic jaundice (author regards diagnosis as somewhat doubtful)	McKendrick, J. S.: Anemia with Enlargement of the Spleen, Practitioner 93:660, 1914	8 yrs. Male	No history of enlargement; Wt., 4.7 oz.; pulp, majority of cells lymphocytes; few normoblasts; considerable nonerythrocytic and eosinophilic polymorphonuclears	Before splenectomy: R.B.C. 2,550,000; Hb. 25%; W.B.C. 7,800; differential normal; anisocytosis; polkioleucosis; polychromatophilic; few normoblasts. After 3 mos.: R.B.C. 4,890,000; Hb. 75%; W.B.C. 12,000; P. 62%; L.M. 5%; megalocytes 6%; no nucleated R.B.C.	22 months after, healthy appearance; no trace of anemia	No history of spleen enlargement; ill health and anemia for 4 years
11. Hemolytic jaundice	Arseultz: Hemolytic Jaundice Cases (see Ellott and Kanavel's table)	13 yrs. Female	No report	No report	Afterward entirely healthy	Had epileptiform attacks 2 days after operation; did not recover
12. Hemolytic jaundice	Giffin, H. Z.: Private communication	9 yrs.	Chronic splenitis	Before splenectomy, 9 days: R.B.C. 1,34; Hb. 24%; W.B.C. 15,200. After splenectomy 18 days: R.B.C. 2,16; Hb. 38%; W.B.C. 12,600	Jaundice from birth; more marked at times; Splen. 1½ yrs. Hist. of jaundice in family; mother's cousin; increased fragility R.B.C. Urine 7 da. pre-op.: Amt. 750; Sp. Gr. 1.013; React. acid
13. Hemolytic jaundice	Ibid	11 yrs.	Chronic splenitis	5 days before splenectomy: R.B.C. 3.39; Hb. 59%; W.B.C. 11,000. After 6 mos.: Hb. 95+% (elsewhere)	Jaundice 6 yrs.; Splen. 6 mos. Hist. jaund. in family; father hemolytic jaundice; increased fragility R.B.C. Urine 5 da. pre-op.: Amt. 930; Sp. Gr. 1.014; React. acid; Alb. 0; neg.
14. Hemolytic jaundice	Ibid	11 yrs.	Chronic splenitis; thick, red fatty firm spleen	Before splenectomy, 11 days: R.B.C. 2.69; Hb. 52%; W.B.C. 9,600. After 21 days: R.B.C. 4.24; Hb. 58%; W.B.C. 5,200	Jaundice from birth; Splen. 6 mos.; no family hist. of jaundice; increased fragility R.B.C. Urine 9 da. pre-op.: Amt. 780; Sp. Gr. 1.024; React. acid; Alb. 2; pus 1
15. Hemolytic jaundice	Ibid	8 yrs.	Before splenectomy, 14 days: R.B.C. 4.0; Hb. 68%; W.B.C. 7,200. After 9 days: R.B.C. 5.37; Hb. 78%; W.B.C. 13,600	Died 2 mos. after operation	Jaundice 1 yr. ago for 1 wk.; pain 3 mos.; no family hist. of jaundice; increased fragility R.B.C. Urine 14 da. pre-op.: Amt. 500; Sp. Gr. 1.012; React. acid; Alb. 0; negative

1. Gaucher's disease	Herman, C., and others: Case of Gaucher's Disease in a Boy 13 Years of Age. Arch. Pediat. 31: 340, 1914	13 yrs. Male	Wt., 1,320 gm.; 27×13×10 cm.; many large endothelial cells with irregular outline; one or more nuclei; round of ovoid venous sinus greatly distended	Before splenectomy: R.B.C. 3,900,000; Hb. 45%; W.B.C. 4,000; P. 48%; L. 50%; E. 2%. After 2 mos.: R.B.C. 3,300,000; Hb. 52%; W.B.C. 15,000; P. 62%; L. 35%; E. 3%	Improved greatly after operation	Enlargement of abdomen at 4 yrs.; at 7 yrs. spleen 8 cm. below umbilicus and 1 cm. beyond navel in median line
2. Gaucher's disease	Friedman, J. F., and Moorhead, J. J.: Splenectomy for Splenomegaly (Gaucher type). Am. J. M. Sc. 147: 213, 1914	3½ yrs. Female	Spleen enlarged 2 yrs. before, slightly; great numbers of large nonnuclear cells throughout, occasionally more than one nucleus in a cell; malignant bodies few	Before splenectomy: R.B.C. 6,200,000; Hb. 85%; W.B.C. 7,000; normal differential. After 10½ mos.: R.B.C. 5,300,000; Hb. 75%; W.B.C. 16,000; normal differential	16 mos. after operation child is reported well and strong	
3. Gaucher's disease	Mandelbaum, F. S.: Contribution to the Pathology of Primary Splenomegaly (Gaucher type). J. Exper. M. 16: 191, 1912	4½ yrs. Male	Spleen found large 1 yr. before operation; alveolar spaces with large cells identical to those of Gaucher's disease; malpighian bodies unusually large size	Before splenectomy: R.B.C. 4,000,000; Hb. 68%; W.B.C. 4,200; P. 70%; L.L. 25%; Mono. 1%; Myelo. 1%; slight leukoerythrosis and anisocytosis. After: R.B.C. 3,800,000; Hb. 66%; W.B.C. 19,600; normal differential	Child died day following operation	
4. Gaucher's disease	Foot, N. C., and Ladd, W. E.: Report on a Case of Gaucher's Splenomegaly. Am. J. Dis. Child. 21: 426 (April) 1921	8 yrs. Male	Spleen 1 cm. below costal margin about 7 yrs. of age; Wt. 305 gm.; 14×6×5; large cells typical of Gaucher's disease, filled the venous sinuses and pulp spaces so completely as to transform the picture into one resembling alveolar tumor	Before splenectomy: R.B.C. 5,808,000; Hb. 90%; W.B.C. 6,600; P. 49%; L.L. 19%; S.L. 30%; Mononu. 3%; 1 myelocyte noted. After: R.B.C. 4,976,000; W.B.C. 18,800; P. 48%; L. 41%; E. 1%; Monos. 10%; R.B.C. normal	4 mos. after operation gained 2 lbs. general health improved; attending school regularly	Fullness in flank noticed about 4 yrs. of age. Symptoms: pain in abdomen and legs and profuse sweating
Unclassified Cases:						
1. Large cell splenomegaly	Jonz, R. de Josselonde and von Heukelom, T. S.: Beitrag zur Kenntnis der grosszellig Splenomegalie. Beitr. z. path. Anat. 48: 598, 1910	12½ yrs. Female	Malpighian bodies and pulp consist of alveolar connective tissue filled with large, irregular shaped cells with one or more nuclei	Before splenectomy: R.B.C. 4,782,000; Hb. 65%; W.B.C. 3,800. After 6 mos.: R.B.C. 4,920,000; Hb. 80.85%; W.B.C. 14,400; P. 54%; S.L. 18.6%; L.L. 10.0%; L.Mono. and T. 6.8%; E. 10%	6 mos. after operation general condition fairly good, but slight jaundice and enlargement of liver	At 7½ yrs. of age abdomen had begun to enlarge; liver and spleen both large
2. Possible hemolytic jaundice	Stiffon, J. Bland: Three Successful Splenectomies. Lancet 2: 974, 1885	5 yrs. Female	Wt. 10 oz.; no pathologic report	None	Recovered and seemed in excellent health	Author believes it to be a case of hemolytic jaundice such as he had seen in an older patient before; no symptoms reported
3. Possible Banti's disease	Thursfield, H., and Gow, A. E.: Splenomegaly. Splenectomy. St. Barth. Hosp. Rep. 50: 7, 1914	10 yrs. Female	No report	Before splenectomy, 18 mos.: R.B.C. 4,630,000; Hb. 72%; W.B.C. 12,000	Died 48 hours after operation	Called "splenomegalic cirrhosis of liver"
4. Enlarged spleen with anemia	Bartling, G.: Splenectomy for Enlarged Spleens with Anemia. Lancet 1: 226, 1913	6 yrs. Female	No report	Before splenectomy: R.B.C. 3,300,000; Hb. 70%; W.B.C. 26,000. After: no count	Died 4th day after operation	Condition of liver after operation suggested delayed anesthetic poisoning
5. Splenomegaly...	Nixon, J. A.: Splenectomy for Splenomegaly. Brit. M. Clin. J. 31: 325, 1913	14 yrs. Female	No history of enlargement until time of first examination; 7×3 in.; enlargement due to simple hyperplasia of normal spleen tissue	Before splenectomy: R.B.C. 5,000,000; Hb. 50%; W.B.C. 17,000; P. 53%; L.Mono. 14%; S.Mono. 28%; E. 5%; no abnormal cells. After 4 mos.: R.B.C. 4,200,000; Hb. 80%; W.B.C. 9,200; P. 52%; S.Mono. 37%; L.Mono. 7%; E. 8%	For a year after operation, remained well; later developed symptoms of pulmonary tuberculosis	Strong and well until 1 year before operation

disease, 4; hemolytic jaundice, 15; tuberculosis, 1; septic splenomegaly, 1; unclassified cases, 5. Splenic anemia and Banti's disease have been classified together because it is generally accepted that the designation "splenic anemia" in most instances probably corresponds to the early stages of Banti's disease.

A study of the case reports would justify the statement that splenectomy had been resorted to in most instances to save life. One wonders if removal of the spleen may not be considered as a measure to conserve life. If this be so a decision to remove it in the early stages of the pathologic processes is important.

Table 2 summarizes the incidence of spleens which extend 2 cm. or more below the costal margin. The measure, 2 cm., is chosen arbi-

TABLE 2.—SHOWING DISEASES AND NUMBER OF CASES OUT OF 2,000 WITH SPLEEN 2 CM. OR MORE BELOW THE COSTAL MARGIN (BABIES' HOSPITAL, NEW YORK CITY)

Diagnosis	No. of Cases	Measurement of Spleen Below Cm.		Average Age, Months	Sex	
		Average	Maximum		Male	Female
1. Tuberculosis, general miliary....	17	2¾	6	12¾	10	7
2. Congenital syphilis	10	4¾	9	5 1/10	1	9
3. Bronchopneumonia	18	2½	5	12¾	10	8
4. Von Jaksch's anemia.....	4	7	9	6	4	
5. Rickets and complications: secondary anemia; bronchopneumonia; asthma; lobar pneumonia	9	2½	5	16	5	4
6. Chronic constipation	1	3	3	19	1	
7. Anemia, secondary and complications: follicular tonsillitis, purpura	5	5¼	7	13 1/10	3	2
8. Sarcomatosis	1	2	2	28	..	1
9. Bronchitis	2	2	2	4½	2	
10. Congenital heart disease.....	3	2	2	7	3	
11. Tonsillitis	1	2	2	4 yrs.	..	1
12. Marasmus and complications: gastro-enteritis; acute bronchitis; secondary anemia; bronchopneumonia	4	2	2	4	3	1
13. Nutritional edema with anemia..	1	2	2	2½	1	
14. Empyema	4	2½	3	10½	3	1
15. Fistula: vesico and rectovaginal	1	3	3	11	..	1
Total number of cases.....	81	46	35

trarily as representing a large spleen. Fifteen diseases are recorded in this tabulation. With the exception of von Jaksch's anemia (possibly, also some of the cases classified under anemia) the other fourteen diseases must be differentiated from those conditions to which splenectomy is applicable. No instance of leukemia appears in this chart. This disease, perhaps above all others, must be excluded in a decision to remove the spleen. Removal of the spleen in leukemia is contraindicated.

Three cases are presented herewith as a contribution to the literature of splenectomy. From an analysis of their history, symptoms and physical signs, an attempt will be made to derive certain criteria, which may aid to indicate under what circumstances splenectomy is justifiable.

REPORT OF CASES

CASE 1.—This case is of special interest as the boy has been since 3 months of age under the care of Dr. F. Elmer Johnson of New York, who referred him to the Babies' Hospital.

History.—T. M. was admitted March 5, 1920, at 5 years of age, for a blood transfusion. Five days before he was admitted it was noticed that he was pale; and two days before his admission he vomited blood, and blood was noticed in his stool.

Family History.—Father and mother are in good health. Two other children are living and well. There is no history of jaundice in the family.

Birth History.—He was full term; the labor was normal, and the birth weight is reported as being 10 pounds.

Feeding History.—He was breast fed for six months after which he received milk and barley water mixtures. At one year he was given solid food. His nutrition was always excellent.

Previous Illnesses.—He was always healthy up to the age of 3½ years when he first vomited blood. The mother stated it was about a cupful. Afterward he became pale and listless and stayed so for six months. He then began to improve and his color returned. When he was 4½ years old he vomited blood again. This time the quantity was said to be larger. He was pale and listless for about three months when he began to pick up and his color returned. At 4 years of age he went to St. Luke's Hospital, New York, because of an attack of diarrhea. He received at the same time radium treatment for an enlarged spleen. He returned to St. Luke's Hospital three times between the ages of 4 and 5 for radium treatment.

After his third treatment, April 30, 1920, he became pale. Three days later he vomited blood and passed black stools. Because of weakness and inability to be up and about he was sent to the Babies' Hospital for transfusion.

The enlargement of the spleen was first noticed at 3 months of age. It measured two inches from the costal margin. Dr. Johnson observed particularly that the spleen was "prominent on the abdominal wall."

Summary of History.—Vomiting of blood occurred, therefore, three times between birth and 5 years of age: first at 3½ years; a second time at 4½ years; and a third time at 5 years. Enlargement of the spleen was first noted when he was 3 months old. Four radium treatments for an enlarged spleen had been given at St. Luke's Hospital within the year before his admission to the Babies' Hospital. They apparently were of no avail in diminishing the size of the spleen nor in checking hemorrhage.

Physical Examination.—General appearance was that of a well developed and well nourished white boy. He was rather pale. Mucous membranes were pale. Heart: Normal in size; the sounds were of good quality; a soft blowing systolic murmur was heard at the apex and along the left border of the sternum. Liver: Not felt. Spleen: Measured 7 cm. from the costal margin to the tip and 7.6 cm. from side to side. In all other respects the physical examination was normal.

Blood Examination, Before Transfusion.—Red blood cells, 3,200,000; hemoglobin, 30 per cent.; white blood cells, 6,000; polymorphonuclears, 70 per cent.; lymphocytes, 30 per cent.

He was transfused May 5, 1920, with 230 c.c. of blood from a cousin.

Blood Examination May 6, 1920 (day after transfusion).—Red blood cells, 4,160,000; hemoglobin, 55 per cent.; polymorphonuclears, 80 per cent.; lymphocytes, 20 per cent.

Marked achromia and slight variation in size of the red cells. No normoblasts nor megaloblasts seen. Pirquet test negative.

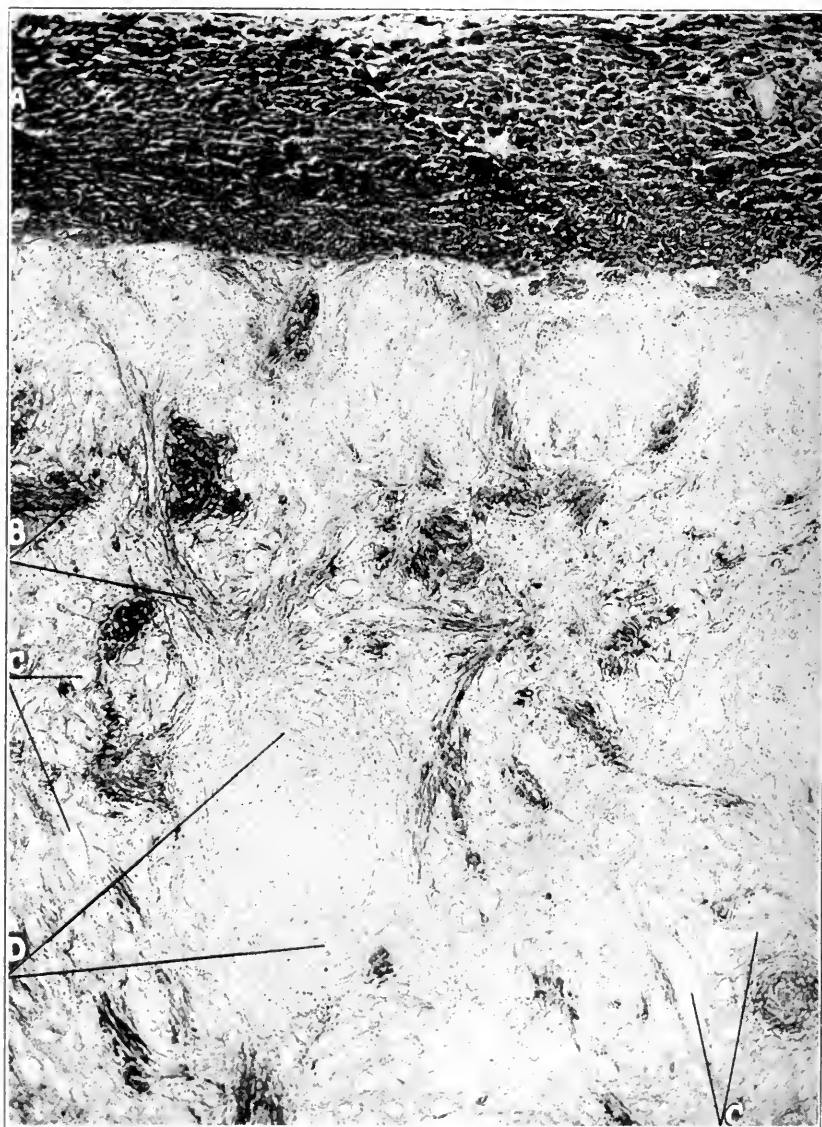


Fig. 1.—Section of spleen of Banti's Disease, Mallory's connective tissue stain. *a*, capsule; *b*, trabeculae; *c*, dilated venous spaces; *d*, malpighian body; $\times 135$.

The temperature on admission was 99; the day following transfusion it rose to 101.4 F; and on the day of his discharge it was 99.6 F.

He was discharged May 7 against advice, with the diagnosis of chronic secondary anemia.

Second Admission.—Nov. 3, 1920, T. M. was readmitted to the hospital. The occasion for his return was "bleeding from the rectum." The statement was made that two days before admission he passed about "half a chamberful of blood." It was estimated that there was about one quart of clotted blood and feces. On the day of admission there was another "bleeding from the rectum."

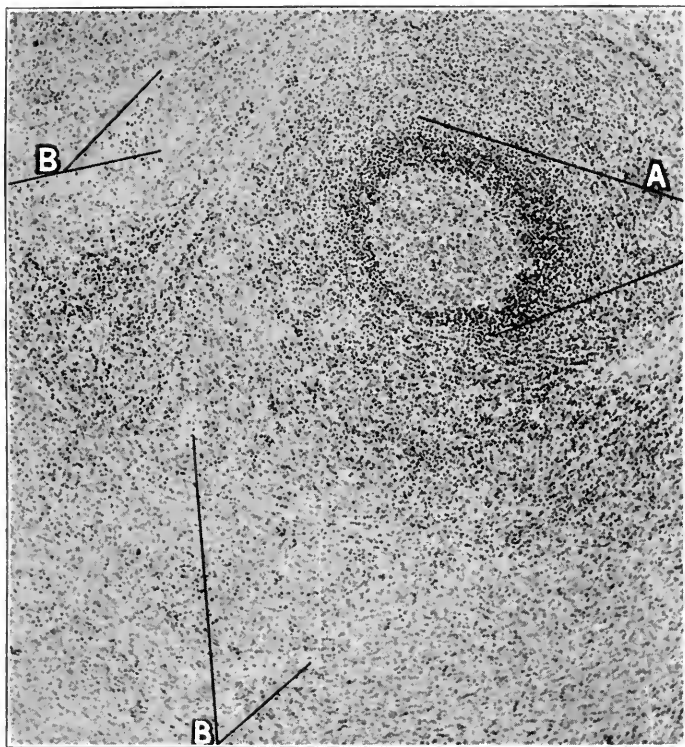


Fig. 2.—Section of spleen of Banti's Disease; a, malpighian body with Keim center; b, dilated venous spaces; $\times 135$.

On his first admission in May no special information was obtained about the loss of blood by way of the rectum. The history obtained at that time was of repeated vomiting of blood. It mentioned casually that tarry stools had been observed.

The first hemorrhage by way of the lower bowel occurred at $2\frac{1}{2}$ years of age. From that time to Nov. 20, 1920, he had about five similar attacks separated by several months' intervals. The losses of blood were, as a rule, repeated over a period of one or two days. He became pale at the time of the attack but would regain color until the next hemorrhage.

The diagnosis on readmission was duodenal ulcer.

The physical examination added only the following information: enlargement of the tonsils and carious teeth. The spleen measured 9 cm. from the costal

margin to its tip; six months before it measured 4 cm. The weight was 49½ pounds. The blood count was as follows: Dec. 1, 1920: Red blood cells, 3,702,000; hemoglobin, 45 per cent.; leukocytes, 4,400; polymorphonuclears, 71 per cent.; lymphocytes, 29 per cent.; small lymphocytes, 22 per cent.; large lymphocytes, 7 per cent. The red cells showed slight acromia. One normoblast was seen in counting 100 white cells. Stool was negative for blood.

December 8: Removal of the spleen was decided on. The reason for this decision was in the nature of a counsel of desperation. The transfusion in May had proved unavailing in preventing a recurrence of the hemorrhages and in determining any improvement in the blood condition.

December 10: Transfusion of 150 c.c. of blood from an uncle.

December 11: Splenectomy by Dr. William Downes. The spleen weighed 375 gm. The liver showed some thickening of the capsule and some enlargement. It was apparently not harder than normal. No ulcers were found in the pylorus or duodenum. The abdomen contained a large amount of fluid which gushed from the wound.

TABLE 3.—RECORD OF BLOOD EXAMINATIONS IN CASE 1

Date	Erythro- cytes	Hemo- globin, per Cent.	Leukocytes	Poly- morpho- nuclears, per Cent.	Lympho- cytes, per Cent.	Transi- tionals, per Cent.	Remarks
12/ 1/20	3,792,000	45	4,400	70	29	1	Red cells show slight achromia; one nor- moblast to 100 leukocytes
12/ 9/20	2,160,000	35	7,800	70	30		
12/10/20	Transfusion				
12/11/20	3,104,000	50	10,000	72	28		Large mononuclears 3% Large mononuclears 7% Large mononuclears 5%
12/11/20	Splenectomy				
12/14/20	3,100,000	50	34,000	76	18	3	
12/17/20	3,824,000	50	13,200	72	28		
12/20/20	4,192,000	60	10,200	49	36	8	
12/23/20	5,168,000	65	17,000	68	32		
12/26/20	4,176,000	70	10,300	64	25	6	
12/30/20	4,224,000	70	10,000	55	45		
1/ 3/21	4,400,000	65	9,800	56	44	..	Discharged on this date
5/16/21	5,192,000	70	10,200	74	26	..	Returned for blood examination 6 mos. after splenectomy. Test for fragility of R. B. C. normal

Jan. 3, 1921: The patient was discharged from the hospital. The convalescence from the operation was most satisfactory. The day following the splenectomy the temperature rose to 104.4 F.; the second day to 102 F.; the third day to 101.4 F.; the fourth day to 101.2 F. From this time on to his discharge the temperature was normal.

Urine Examination.—Repeated examinations showed a normal urine. No tests for urobilin were made. Pirquet test was negative. Wassermann was negative.

The condition of the child May 16, 1921, five months after operation has been kindly furnished by Dr. F. Elmer Johnson in the following personal communication:

The child came to me first on June 7, 1917, at 3 months of age. The first examination revealed a spleen two inches below the costal margin. It was very hard. The baby weighed 11½¹⁰/₁₆ pounds. A Wassermann test June 18, 1915, was negative. July 13, 1915, at four months of age, the leukocyte count was as follows: Total leukocytes, 15,000; polymorphonuclears, 15 per cent.; lymphocytes, 84 per cent.; eosinophils, 1 per cent.

May 13, 1915, the spleen was smaller. It was a question whether the mass felt was a kidney or a spleen. Oct. 25, 1915, he weighed 19 pounds. Sept. 26, 1915, he weighed 26 pounds; the hemoglobin was 30 per cent.

May 16, 1921, six months after splenectomy, the patient reported to me. He was in excellent condition. His color was that of a normal child. The mother says he behaves like a normal child except for an abnormal appetite, and restlessness at night.

PATHOLOGIC REPORT (contributed by Dr. Martha Wohlstein): *Macroscopic Examination.*—The spleen weighs 375 gm. and measures 14x8x4 cm. Its capsule is greatly thickened, grey in color, and covered with dense fibrous adhesions most numerous at the upper pole. The uncut spleen felt soft.

On section the capsule is found to measure 1 mm. in thickness. The cut surface of the splenic substance is dull red in color, smooth, rather soft and almost pits on pressure. Connective tissue septums are numerous, grey, not wide. The blood vessels are large. No areas of hemorrhage are apparent,

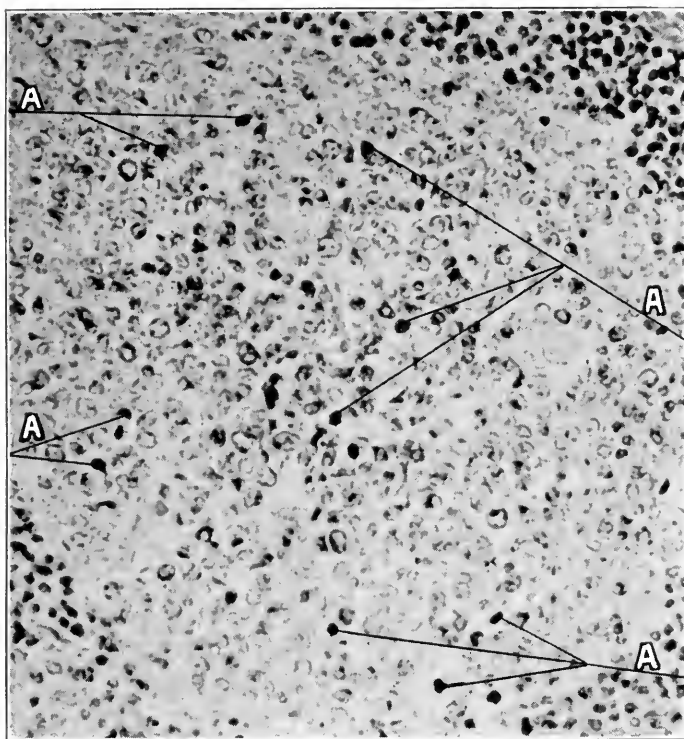


Fig. 3.—Section of spleen of Banti's Disease; Keim center of malpighian body showing kariokynetic figures in nuclei of leukoblasts, *a*; $\times 450$.

but some congested vessels have been cut across. The malpighian bodies show as pearly grey nodules 1 mm. in diameter, and not diminished in number.

Microscopic Examination.—(Figs. 1, 2 and 3).—The capsule is fully three times thicker than normal, and composed of dense fibrous connective tissue. Blood vessels are numerous near the free surface, and small hemorrhages have occurred where these vessels were torn on removal of the organ. From the thick capsule wide trabeculae of connective tissue ramify into the spleen substance. This seems to be made up chiefly of connective tissue and venous spaces, the pulp cells being almost entirely absent from large areas. The venous spaces are dilated in many places, but not beyond a moderate degree. They contain red blood cells, mononuclear and polynuclear leukocytes, and are

lined with endothelial cells. In some places these lining cells are swollen, but they are not found free in the lumen of the blood sinuses. No mononuclear cells resembling those typical of Gaucher's splenomegaly are present, nor are the venous spaces dilated to form the alveolar arrangement typical of that lesion. With Mallory's connective tissue stain the increased amount of fibrous tissue is well shown, and the ramifications of the fibrils about the bodies are large and not less numerous than normal. Each contains a distinct germ center in which from 1 to 3 karyokinetic figures in the nuclei of leukoblasts are present. The periphery of the malpighian bodies is densely packed with mononuclear cells. Some columns of typical pulp cells are seen close to malpighian bodies.

The characteristic things about the sections are three: the marked increase in fibrous connective tissue in the capsule and in the spleen substance; the congested venous spaces; the comparatively small number of pulp cells.

The picture closely resembles that of Banti's disease.

Before presenting the second case of this series, a brief report of a case of von Jaksch's anemia with microphotographs of the spleen is introduced for comparison with Case 1. The diagnosis of von Jaksch's disease was made on the blood picture which was regarded as characteristic of that disease, and on enlargement of the spleen. The latter organ was described as follows: At the level of the umbilicus it reaches to within 1 cm. of the midline. The lower border extends 1 cm. below the level of the crest of the ileum. The blood picture was:

Oct. 10, 1917: Red blood cells, 1,472,000; hemoglobin, 9 per cent.; white blood cells, 83,000; polymorphonuclears, 23 per cent.; lymphocytes, 2 per cent.; small lymphocytes, 75 per cent. Numerous normoblasts showing mitosis, poikilocytosis, anisocytosis, myelocytes.

Oct. 11, 1917, the child was transfused with 60 c.c. of its father's blood into the sinus. The blood picture on the next day showed:

Red blood cells, 1,784,000; hemoglobin, 15 per cent.; polymorphonuclears, 48 per cent.; large lymphocytes, 2 per cent.; small lymphocytes, 45 per cent.; myelocytes, 3 per cent.; eosinophils, 2 per cent. Normoblasts showing mitosis; megaloblasts; poikilocytosis and anisocytosis.

The infant died the following day.

Dr. Martha Wohlstein has furnished the following report on the pathologic examination of the spleen:

Microscopic Examination.—The capsule is of normal thickness; the connective tissue trabeculae are not wider than normal, and they are loosely meshed. The pulp spaces are prominent, some are empty, some contain red and white blood cells. None are closely packed, but in all nucleated red cells are numerous. The endothelial cells lining the veous spaces are distinct and normal. The pulp cells are not increased in number. The malpighian bodies are present in normal numbers, but they are less dense and smaller than usual. No germ centers are apparent in them.

The following points are characteristic of these sections: Small loosely put together or "rarified" malpighian bodies, congested venous spaces, containing numerous nucleated red blood cells; pulp cells less numerous than normal.

Dr. Wohlstein has also placed in parallel columns a comparison of the microscopic pathology of the spleen of Case 1 (Figs. 1, 2 and 3) and of the spleen of the case of so-called von Jaksch's anemia (Figs. 4 and 5).

BANTI'S DISEASE (Figs. 1, 2 and 3)	VON JAKSCH'S ANEMIA (Figs. 4 and 5)
No leukocytosis; blood picture of secondary anemia.	Leukocytosis moderate or very high. Nucleated red cells numerous.
Spleen moderately enlarged.	Spleen moderately or greatly enlarged.
Surface of spleen irregular; capsule thickened.	Surface of spleen smooth, capsule not thickened.
Connective tissue trabeculae much increased; fibrous mesh work dense.	Connective tissue trabeculae increased; fibrous meshwork loose.
Venous spaces dilated; endothelium normal; contents red and white blood cells.	Venous spaces dilated; endothelium normal; contents: leukocytes and many red blood cells.
Splenic pulp cells less numerous than normal.	Splenic pulp cells less numerous than normal.
Malpighian bodies small, less numerous than normal; "Keim" centers with normal leukoblasts.	Malpighian bodies small and rarefied; no "Keim" centers apparent.
Ascites and hepatic cirrhosis in late stage.	No ascites. Liver moderately enlarged; no cirrhosis.

These two pictures may well be two stages of the same pathologic process.

Attention is called to the microscopic examination of the spleen in Case 2 (page 300). Dr. Stout, who reported the examination, states:

This is characteristic of Banti's disease. If, however, the child shows a blood picture of von Jaksch's anemia, the splenic picture would fit but atypically. A positive diagnosis cannot be made without the blood report.

The anomalous situation in the same child is presented of a spleen which records the changes belonging to Banti's disease, and a blood picture characteristic of von Jaksch's disease. If the two cases are a distinct entity, the logic of this situation forces one to accept this proposition: the causative agent of von Jaksch's disease has elaborated its effects in the hemopoietic system; the causative agent of Banti's disease has elaborated its effect in the spleen. The following statement of Krumbhaar is of interest in this connection:

The anemia infantum pseudoleukaemica of von Jaksch is in all probability not an independent condition, but represents an atypical response of the infantile hemopoietic system to one or the other of the primary diseases of the blood.

It has seemed best to interrupt the plan of the paper by this discussion of von Jaksch's disease. It has been stated that von Jaksch's disease is sub judice. This discussion is for the purpose of explaining that declaration.

CASE 2.—T. R. was a patient at St. Mary's Free Hospital for Children, New York City. Dr. Charles Farr has kindly furnished the hospital records for inclusion in this paper.

History.—T. R., a female child, was admitted to St. Mary's hospital Oct. 19, 1917, at 9 years of age. The chief complaint for which she came was swelling of the abdomen. The enlargement was first noticed when the child was about 3½ years of age.

Family History.—The father and mother and seven brothers are alive and well.

Previous History.—The patient had been perfectly well until she was between 3 and 4 years of age when it was noticed that her abdomen began

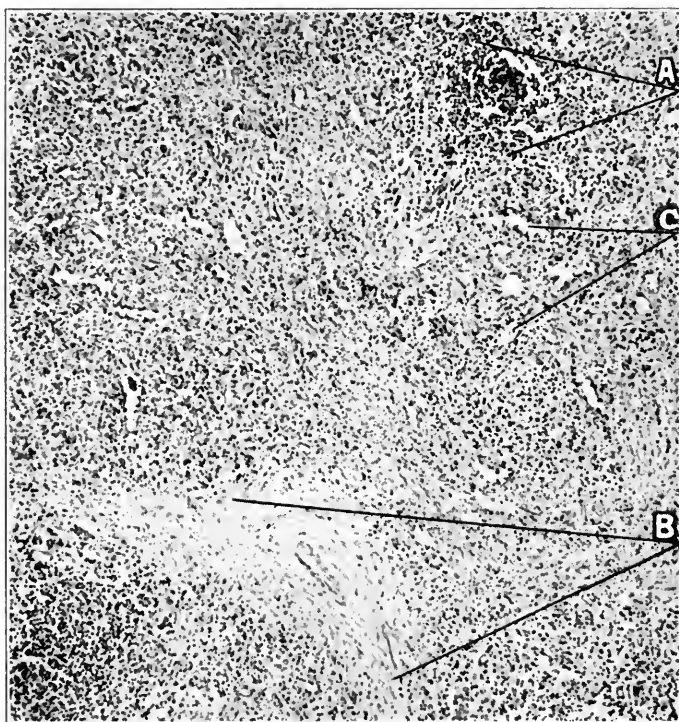


Fig. 4.—Section of spleen from case of von Jaksch's anemia. *a*, Malpighian body; *b*, connective tissue trabeculae; *c*, dilated venous spaces; $\times 135$.

to swell. She came to the hospital June 13, and again July 16, 1917, and on each occasion her abdomen was tapped. The fluid reaccumulated. As there was no dyspnea nothing further was done until the child returned to the hospital Aug. 10, 1917, when an exploratory laparotomy was done. The belly wall was thin; the liver was small; there was no sign of cirrhosis. The spleen was enlarged and bound down everywhere by adhesions. A large mass lay over the pancreas, the relations of which were not determined. The abdomen held a large amount of fluid which was opalescent in color and clotted on standing.

The child was discharged and returned to the hospital for a third time, Oct. 19, 1917. The diagnosis at this admission was tuberculous peritonitis.

Physical Examination.—In general appearance she was much emaciated and looked chronically ill; face was pale and there were deep furrows under the eyes.

Mucous membranes were pale. Teeth, carious, some missing. Tongue was furred and breath was offensive. Thorax was small and there were distended veins over the chest wall. Heart and lungs showed no abnormal signs. Abdomen: Much distended; greater in size than that of a pregnant woman (relatively). The veins in the abdomen wall were much distended. The child had to bend backward to maintain equilibrium. Fluid wave was present. Diagnosis based on physical examination was tuberculous peritonitis.

Treatment.—Oct. 19, 1917: A splenectomy was done by Dr. Charles Farr. The spleen was tremendously hypertrophied. The lower third lay behind the splenic flexure of the colon. The spleen was adherent at the upper pole to the

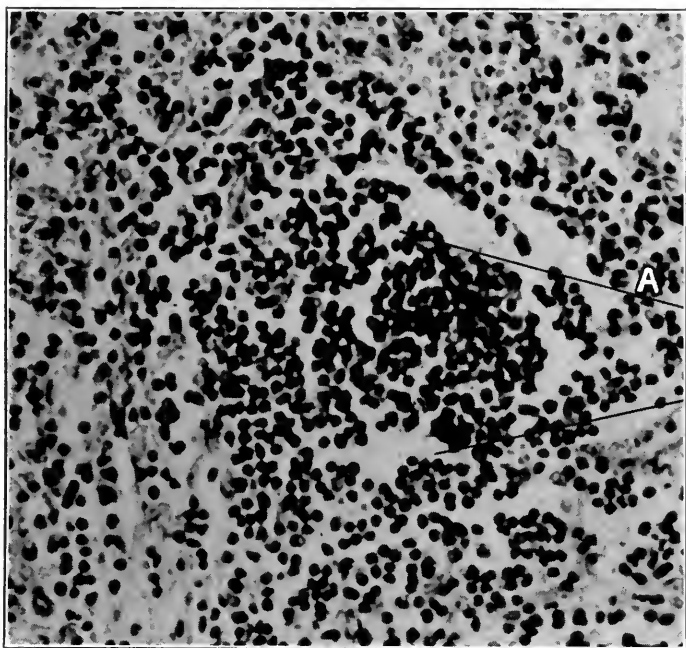


Fig. 5.—Section of spleen from case of von Jaksch's anemia. *a*, Malpighian body; *b*, dilated venous spaces containing many nucleated red blood cells; $\times 425$.

stomach and diaphragm. On delivery the pedicle was torn and severe hemorrhage followed. The vessels were clamped and ligated. Recovery was uninterrupted.

Dec. 12, 1917: Discharged improved.

Diagnosis.—Primary splenomegaly (Banti's).

Urine Examination.—Repeated tests were negative. No mention was made of tests for urobilin.

Pirquet test was negative.

REPORT OF PATHOLOGIC EXAMINATION OF THE SPLEEN

Gross Examination.—The spleen measures 20x7x5 cm. The consistency was soft; the capsule was thickened. Recently found adhesions covered the organ. Cross section showed a pultaceous, red pulp with moderately thickened septums

and somewhat indistinct follicles. Increase in size of the spleen was due to hyperplasia of the pulp and of connective tissues.

Microscopic Examination.—Connective tissue was markedly increased throughout the pulp. The follicles were very small and far apart. The trabeculae were much thickened; the capsule was thickened and showed hyaline degeneration.

The pulp showed large and small lymphocytes and some swollen endothelial cells lining the capillaries. No myelocytes were found. This is characteristic of Banti's disease. If, however, the child shows a blood picture of von Jaksch's anemia the splenic picture would fit but atypically. A positive diagnosis cannot be made without the blood report (Dr. Stout).

TABLE 4.—RESULT OF BLOOD EXAMINATIONS IN CASE 2

Date	Erythrocytes	Hemoglobin, per Cent.	Leukocytes	Polymorphonuclears, per Cent.	Lymphocytes, per Cent.	Transitionals, per Cent.	Large Mononuclears, per Cent.	Basophils, per Cent.	Eosinophils, per Cent.	Remarks
8/ 3/17	4,340,000	68	3,600	72	19	..	4	2	3	R.B.C. pallor marked.
9/ 7/17	3,440,000	65	5,800	62.7	18.2	1.8	12.7	1	3.6	Poikilocytosis
10/ 4/17	3,968,000	..	4,100	65	31	1	..	2	1	R.B.C. pallor marked.
10/17/17	3,200,000	65	6,000	67	28	2	3			Polychromatophilia.
10/19/19	Splenectomy							Poikilocytosis
10/28/17	2,700,000	56	25,600	80	17	2	1			
11/ 2/17	25,000	73	19	3	5			
11/ 4/17	3,000,000	55								
5 18/21	6,240,000	70	9,800	45	40	6	5	..	4	This count is about 3½ years after splenectomy

ANALYSIS OF CASES 1 AND 2 WITH REFERENCE TO CRITERIA FOR SPLENECTOMY

The pathologic examination of the spleens of both these cases shows the changes which belong to Banti's disease. They will, therefore, be discussed together. An attempt will be made to select the salient points which collectively serve as a guide in a decision to remove the spleen.

Age of Onset.—It is impossible to state with definiteness in either case the time when the disease began. If an enlarged spleen is evidence that an abnormal condition exists the statement may be hazarded that the first stage of Banti's disease was present in Case 1 at 3 months of age.

Textbooks place the onset of Banti's disease late in childhood. "The onset is late in childhood, usually not before the tenth year, and the progress is slow (Holt)."

It seems reasonable to assume that the enlargement of the spleen in Case 1, noticed at 3 months of age, was determined by the abnormal processes which later, at the age of 3 or 4 years, manifested themselves

in the symptoms and physical signs which the pathologic examination of the spleen proved to be those of Banti's disease. It would seem absurd to assume that the enlargement of the spleen at three months was in response to an abnormal stimulus which is distinct from that which causes Banti's disease in view of the fact that the same spleen which was removed when the child was $5\frac{1}{2}$ years of age, showed the changes belonging to Banti's disease. It seems probable that this spleen at $3\frac{1}{2}$ months of age was the precursor of the later spleen.

T. R. (Case 2), had an exploratory laparotomy done when she was 9 years of age. The spleen was found to be enlarged. There is no history that the spleen was felt before that date. The abdomen began to swell when the child was between 3 and 4 years of age. The child was tapped at that time and fluid withdrawn. The ascites which was present was doubtless related to the same causes which produced the enlarged spleen. The onset in Case 2 was probably as early as $3\frac{1}{2}$ years of age.

Therefore, Case 1 presents a probable onset at 3 months of age, and Case 2 at about $3\frac{1}{2}$ years of age.

Attention is called to the possibility of an early onset of Banti's disease. If a splenectomy for this condition offers hope of a cure, the operation should be done before the advanced changes have taken place in the liver. May one be sure that an early splenectomy will forestall the cirrhotic changes in the liver? This assurance cannot be made. It may, however, be stated that a splenectomy, even after the disease has progressed to the late stage, results in an improvement in both symptoms and physical signs in a certain number of individuals, and that a splenectomy done in the early stages of the disease may, at least, delay the progress of the disease with its associated symptoms of hemorrhage, ascites, anemia, etc.

It is not known what part the spleen plays as a causative factor in Banti's disease.

The unquestioned improvement that usually follows splenectomy indicated that the altered spleen is in some way an important pathogenic factor. This is still further emphasized by Umber's unique observation. A boy, 15 years of age, was splenectomized for Banti's disease, and during the operation a small piece of the enlarged liver was excised for histological examination and a distinct peripheral infiltration of the lobules found. Later the liver reduced to normal size, a strong indication of the splenogenous origin of the hepatitis, which, if undisturbed, should have progressed to the usual cirrhosis (Krumbhaar¹).

Enlargement of the Spleen.—The tip of T. M.'s spleen (Case 1) was felt 5 cm. below the costal margin when he was 3 months of

1. Pearce, M. P.; Krumbhaar, E. B., and Frazier, C. H.: *The Spleen and Anemia, Experimental and Clinical Studies*, Philadelphia, J. B. Lippincott & Co., 1918, p. 251.

age. T. R.'s spleen (Case 2) was found to be enlarged when her abdomen was explored at about 8½ years of age.

The histologic examination of both spleens showed the changes belonging to Banti's disease (Figs. 1, 2 and 3 for T. M.'s spleen).

The diseases with which enlarged spleens are associated are analyzed in Table 2. From an examination of this table it will be seen that enlarged spleen is associated with a large number of abnormal conditions.

It is impossible to define the phrase "an enlarged spleen." If the edge of the spleen is felt just below the costal margin, the spleen is larger than normal. If the edge of the spleen is felt 2 cm. or more below the costal margin, it certainly is a warning to determine the pathologic condition with which such an enlargement is associated. The importance of such determination is obvious since indications for the removal of the spleen are limited. It becomes necessary, therefore, to exclude a large number of diseases with which splenomegaly is associated before considering splenectomy.

Emphasis is made: *First, that a distinctly enlarged spleen may be part of a pathologic condition the relief or cure of which depends on the removal of the spleen; and second, that such an enlargement may be present in the first year of life.*

BLOOD EXAMINATION: Anemia.—A study of blood examinations of Cases 1 and 2, shows in each instance a diminution of the number of erythrocytes, a hemoglobin percentage below normal, and a leukopenia. The erythrocytes showed poikilocytosis, polychromatophilia, and marked pallor.

These blood findings define a secondary anemia. This type of anemia is characteristic of Banti's disease.

Evidence of blood destruction furnished by the erythrocytes (poikilocytosis, etc.) is regarded as an indication that the disease is progressive. Therefore, blood destruction without active blood regeneration (normoblasts, reticulated erythrocytes, Howell-Jolly bodies, etc.) following transfusion furnishes a point in favor of splenectomy in the pathologic condition represented in these cases.

A leukopenia is usually associated with secondary anemia in Banti's disease; it was present in both cases.

When T. M. (Case 1) was 18 months old, Dr. Johnson found the hemoglobin to be 30 per cent. This observation is significant. At 18 months of age, therefore, there was a combination of splenomegaly and anemia. No erythrocyte count was made at this time.

A leukocyte count was made when the child was 6 months of age showing the total to be 15,000 cells of which the lymphocytes were 84 per cent. The increase of leukocytes at this period in association with an enlarged spleen might suggest von Jaksch's disease. This is

further emphasized by the predominance of lymphocytes. On the other hand, the fact that T. R.'s spleen showed characteristics of Banti's disease might throw doubt on the existence of von Jaksch's disease as a distinct entity. A comparison of the histology of Banti's disease and von Jaksch's disease is furnished in the accompanying illustrations.

It is not intended to postulate that von Jaksch's and Banti's disease are identical by the citation of the leukocyte count of T. R.'s blood when he was 6 months old. Attention is called to it in the hope that further information may be forthcoming.

The effects of transfusion on T. R.'s anemia is shown in Table 4. The erythrocytes rose from 3,200,000 to 4,160,000; the hemoglobin from 30 to 55 per cent. The child was taken from the hospital to return in seven months, at which time the red blood cells numbered 3,702,000 and the hemoglobin 45 per cent. As this blood count was made after hemorrhages from the intestines, it gives no information as to whether the increasing anemia was due to losses of blood or whether it was evidence of persistent blood destruction associated with the disease itself.

Independent of this case, it is important that, following repeated transfusions, improvement in an anemia is only temporary. The interpretation of a transitory improvement in the blood is that the agent determining blood destruction is dominant. Consequently, a combination of persistent blood destruction and of an enlarged spleen in spite of repeated transfusions furnishes a good starting point for serious consideration of splenectomy.

It is desirable that a thorough search for evidence of blood regeneration as well as of blood destruction be made when one is confronted with the problem of splenectomy.

Evidences of

Blood Destruction	Blood Regeneration
Polychromatophilia	Increased erythrocyte count.
Microcytes	Increase of percentage of hemoglobin
Poikilocytes	Following transfusion an increase in
Diminished blood platelets	reticulated red cells; Howell-Jolly
Leukopenia	bodies; Cabot ring forms
Increased urobilin in urine and stools	Blood platelets normal or increased.

The successive blood counts made after splenectomy in both cases are recorded in their respective charts. The erythrocytes steadily increased in number in both children. T. M. (Case 1) showed a count of 5,192,000 six months after the splenectomy. The hemoglobin was also increased but not in like degree. In both children, however, the hemoglobin may be regarded as within normal limits for their age.

A leukocytosis followed the splenectomy in both cases. This is the usual reaction following splenectomy and indicates a favorable response of the blood forming organs. The later leukocyte counts correspond to the normal for children of their age.

Studies of the blood after splenectomy furnish a good index of the degree of improvement in the condition for the relief or cure of which the spleen was removed.

Hemorrhages.—T. M. (Case 1), had his first hemorrhage at 2½ years of age. The blood was evacuated by way of the rectum. "Bleeding from the rectum" was repeated several times during the following three years. He first vomited blood when he was 3½ years old. This was repeated twice in the following two years.

The repetition of hemorrhages, the persistence of anemia, in spite of transfusion, and the failure of radium to reduce the size of the spleen, were the chief reasons for deciding to do a splenectomy. Hemorrhages may, of course, occur from other mucous membranes than those of the gastro-intestinal tract. The occurrence of hemorrhages indicates that the pathologic process has involved tissues outside of the spleen. It is unfortunate to delay splenectomy until such a startling warning occurs. The proper time for the removal of the spleen is, therefore, in the early stages of the disease.

Splenectomy in the first stage (Banti's disease) is not only accompanied by a lower mortality but in the great majority of cases has caused great and lasting improvement in the system, often amounting to a complete cure. When the third stage is reached, with permanent changes in the liver and circulatory system, not only is the operation most dangerous, but the chances for improvement are greatly lessened. . . . Nevertheless, the prevalent opinion is probably correct that the improvement that follows splenectomy in the early Banti's disease, in the great majority of cases, either amounts to a complete cure or persists without relapse for many years. Even in the third stage, splenectomy may be of value (Krumbhaar¹).

Ascites.—T. R. (Case 2) presents an accumulation of fluid in the abdomen as evidence of an advanced stage of Banti's disease. The swelling in the abdomen, which was noted when she was between 3 and 4 years of age, was probably due to the fluid. About five and a half years later the abdomen was tapped and fluid drawn. This procedure was followed within a month by an exploratory laparotomy which disclosed a much enlarged spleen and a large amount of fluid in the abdomen. Two months later the spleen was removed. Three and a half years after splenectomy there was no evidence of fluid and no return of anemia. As stated above this case offers evidence of the improvement following splenectomy in the late stages of Banti's disease.

It is important, however, to remove the spleen in the early stages of the disease. An early splenectomy may prevent or postpone the

advanced pathologic changes of which hemorrhages and ascites are manifestations. Splenectomy should not be delayed until hemorrhages and ascites appear.

RESULTS OF TREATMENT: *Radium*.—The repeated treatments by radium of the enlarged spleen in the case of T. M. (Case 1), were of no help. The spleen was not reduced in size and the hemorrhages were not checked. At present it may be said that radium treatment has been of no avail in the treatment of Banti's disease.

Blood Transfusion.—The results of the transfusion of blood offer most important information in forming an opinion as to whether or not a splenectomy should be done. The assistance which blood transfusion offers in the problem under discussion may be stated as follows: If an infant or child has an enlarged spleen with a blood picture of secondary anemia and with evidence of blood destruction and if he receives two or more blood transfusions at intervals of a month without improvement in the blood condition, such an infant or child becomes the potential subject of a splenectomy.

Reference has already been made to the importance of excluding leukemia as a cause of an enlarged spleen. The typical forms of leukemia present little difficulty. It often requires serious study to exclude atypical forms of the disease. The determination of malaria, syphilis and tuberculosis as a cause of splenic enlargement offers less difficulty. A splenectomy in these diseases is contraindicated. If leukemia, malaria, syphilis, etc. (Chart 2), can be excluded, the indications for splenectomy under the conditions stated above, become definite.

The following case of Gaucher's disease furnishes no added criteria to assist one in a decision to do a splenectomy. The chief point of interest in this condition is that the spleen may attain a size greater than that of any of the diseases to which a splenectomy is applicable. As the pathologic condition probably develops simultaneously in the spleen, bone marrow, lymph nodes and elsewhere, there is little hope for permanent relief of symptoms. The operation has, however, been accompanied by temporary relief of symptoms. It must be remembered that a definite diagnosis of Gaucher's disease is almost impossible. The enlarged spleen and anemia, and the failure to secure permanent improvement by transfusion are sufficient criteria for removal of the spleen, assuming that definite causes for the splenic enlargement have been excluded. If one waits to give a definite name, e. g., Banti's disease, Gaucher's disease, to the condition to which an enlarged spleen is associated, there will be no occasion for splenectomy.

CASE 3.—The details of this case were supplied by Dr. William Downes from his service at St. Luke's Hospital, New York. G. B., 6 years of age, was admitted to St. Luke's Hospital July 26, 1919.

Chief Complaint.—Enlarged spleen.

Family History.—Negative.

Birth History.—Full term; normal delivery.

Previous Illnesses.—Has had measles, mumps, and pertussis. No other illness.

Present Illness.—When patient was about 1 year old the mother first noticed a lump in the left side under the ribs. A physician pronounced it a large spleen and said the child would "grow with it." Since then the spleen has increased in size until it fills the abdomen. Mother thinks patient's arms and legs have gotten thinner of late. No loss of weight. Once in two or three months patient has nose-bleed, which usually occurs during sleep. Mother does not think more than a teaspoonful or so of blood is lost. Bleeding stops very readily.

Physical Examination.—General appearance was that of a well nourished child of 6 years, not acutely ill. Only very slight adenitis.

Lungs and Heart: Apparently normal.

Abdomen: Liver very much enlarged. Absolute dulness to the fifth rib posteriorly and sixth rib anteriorly. Lower margin $3\frac{1}{2}$ inches below the costal margin in nipple line. The spleen extends from the rib margin to the pubes on left side. In the right side the edge of the spleen is $2\frac{1}{2}$ inches from the right anterior superior spine of the ilium.

July 26: One hundred and twenty mg. radium in 2 mm. lead and 3 cm. gauze to anterior and lower portion of the spleen for six hours.

August 2: One hundred mg. radium (as above) to left side of spleen for six hours.

August 30: One hundred and thirty mg. radium to upper anterior surface of spleen for six hours.

September 8: One hundred and thirty mg. radium in 2 mm. lead and 2 cm. gauze to side of spleen for six hours.

October 10: One hundred and thirty mg. radium applied to each of four areas of spleen for six hours.

October 12: Patient was discharged with condition practically unchanged.

Nov. 3, 1920: Patient was readmitted on this date. Since last admission patient has had occasional slight hemorrhages from the nose but felt in usual health and gained $2\frac{1}{2}$ pounds. Appetite was fair. Seven weeks ago went to school; when she returned she complained of pain in left side of abdomen so went to bed. Magnesia was prescribed and bowels moved with relief. The next night had a severe hemorrhage from nose; this was repeated the next day and the doctor was called. The nose was plugged and the hemorrhage stopped. Since then she has had a weekly recurrence of hemorrhage, some severe. Thromboplastin usually stopped the hemorrhage. She was able to walk around while at home, and except for occasional headache had had no complaint.

Physical Examination.—General appearance was that of a poorly nourished, underdeveloped, and anemic white girl. Expression dull but mentally bright and observant. Face is pale. Lips and nostrils show dried blood evidently from recent hemorrhage. Neck: There is a marked bilateral systolic pulsation seen. There is a large palpable cord seen on the left side of the neck not pulsating and not tender. A few enlarged glands felt at angles of the jaw. Thorax: Measures 59 cm. in circumference at level of nipples. Marked emaciation with prominent external mammary veins anastomosing below the superficial epigastric veins. Lower part of thorax flares markedly and yet is symmetrical. Lungs: Apex beat felt fourth space in recumbent position, 7 cm. to left of midsternal line. No thrill palpable. At apex, sounds are loud and rough and valvular. There is a short, low systolic murmur heard best at junction of fourth left rib with sternum, but also over apex, but not trans-

mitted to axilla. At base, systolic murmur heard over aortic and pulmonic areas transmitted to neck. Pulse rate 134, regular, poor volume, well sustained and of good force.

Abdomen: Measures 70.5 cm. at level of umbilicus, very prominent; skin pale, veins prominent. Liver extends 8 cm. below costal arch in right mammary line. Spleen extends 7 cm. to right of umbilicus and down into pelvis.

November 6: Blood transfusion given; 13 ounces of citrated whole blood.

November 9: Condition about the same. Patient had slight bleeding from the nose last night.

November 15: Patient was transferred to surgical service. Age, 7 years.

Diagnosis.—Splenic anemia.

Treatment.—November 16: Operation, splenectomy. Operator, Dr. William Downes. Patient died the same day.

Pathologic Findings at Operation.—The spleen was enormously enlarged, being nearly the size but not the contour of the average adult liver; it was mottled with dark purplish spots, somewhat scarred looking areas. It was adherent to the stomach and liver at its upper pole. On its upper and outer surface was an area 4 by 6 inches yellowish, soft, necrotic, and partially broken down in the form of an abscess. The veins of the hilus of the spleen were enormously dilated.

TABLE 5.—RESULT OF BLOOD EXAMINATIONS IN CASE 3

Date	Erythro- cytes	Hemo- globin, per Cent.	Leukoocytes	Poly- morpho- nuclears, per Cent.	Lympho- cytes, per Cent.	Remarks
7/26/19	2,100,000	50	4,000	38	62	Moderate anisocytosis and poikilocytosis; one normoblast seen
8/ 8/19	8,700	60	40	Anisocytosis, poikilocytosis, polychromatophilia, Howell-Jolly bodies
10/ 3/20	840,000	19	2,800	75	24	Patient readmitted, having been at home over a year
10/ 6/20	740,000	17	Trans- fusion	13 oz. citrated whole blood given intravenously
10/ 6/20	
10/ 7/20	2,000,000	20	2,000	78	32	Slight bleeding from nose last night; condition about same
10/ 9/20	1,100,000	24	
10/10/20	24	Trans- fusion Splenectomy	300 c.c. of citrated whole blood given intravenously Died same day
10/12/20	1,100,000	25		
10/14/20	
10/16/20	Splenectomy	

Operative Procedure.—Peritoneal cavity opened and the pathology of the spleen noted; it was free from adhesions to the liver and stomach. An opening was made into the abscess over the necrosed portion; pus and necrotic material were aspirated. The lower lobe of the spleen delivered out of the wound, the vessels at the hilus clamped and the organ excised.

Urine Examination.—Nov. 3, 1919: negative.

Pirquet test not made.

Wassermann: Aug. 8, 1919, negative.

Blood for grouping, Nov. 3, 1920, Group III.

REPORT OF PATHOLOGIC EXAMINATION OF THE SPLEEN

Macroscopic Examination.—Specimen consists of a spleen measuring 30x16x9 cm. and weighing 1900 gm. The capsule is smooth, except over one or two small areas on the inferior surface overlying a large area of infarction. The latter crosses the anterior surface forming a broad, irregular but sharply defined

yellow area from 6 to 8 cm. wide and penetrating into the substance from 2 to 5 cm. Other yellowish plaques, smaller and ever more irregular, are found toward the upper pole. The vessels at the hilus are small and surrounded by about ten lymph nodes, all soft, dark red and resembling the spleen itself. Their capsules are thin and soft. On section it shows the uniform porphyry red color, all the normal markings being obliterated. The surface is smooth, cellular and dull without large vessels.

Microscopic Examination.—Sections of the spleen show no normal tissue, there being only a few flattened cords representing the original structure and a few fibrous trabeculae. The morphology is uniformly altered by the extreme dilation of the sinuses, which are distended to form rounded alveoli, lined with and partially filled with small eccentric rounded nuclei. These cells are rather granular, some of them distinctly pigmented with fine yellowish granules distributed throughout the cytoplasm uniformly.

Diagnosis.—Gaucher's disease.

It does not come within the scope of this paper to give an exposition of hemolytic jaundice. It is sufficient to state that of those conditions to which splenectomy appertains, hemolytic jaundice, familial or acquired, offers the greatest hope of a cure by removal of the spleen.

The problem in this disease, as far as it relates to splenectomy, is quite the same as in Banti's or Gaucher's disease. The decision to remove the spleen is based on the presence of a large spleen, persistence of a secondary anemia after repeated blood transfusions, and a physical disability which make the individual a chronic invalid. Hemolytic jaundice has the advantage of a distinguishing sign in the icterus. This is a great aid in stimulating interest in an explanation of the jaundice. If the term "Haemolytic jaundice" fits the condition, one is in a position to assert that splenectomy offers the best chance of curing the disease.

CONCLUSIONS

1. The conditions for which relief or cure by splenectomy may be indicated are present in the first years of life more frequently than is generally accepted.

2. It is desirable to remove a spleen in the early stages of the pathological process for which splenectomy is indicated.

3. Hemolytic jaundice presents the most favorable condition for cure by splenectomy.

4. Banti's disease and Gaucher's disease represent pathologic processes for which splenectomy may give relief of symptoms and may serve to prolong life.

5. Von Jaksch's disease is probably not an independent condition.

6. Indications for the removal of the spleen depend on certain criteria, not on the making of a definite diagnosis. These criteria are splenomegaly, secondary anemia, and the failure of repeated blood transfusions to determine any improvement in the anemia and general condition.

THE BACTERIOLOGY OF THE NORMAL INFANT'S URINE *

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It has been rather generally accepted that the urine of normal infants often contains a small number of organisms that cannot definitely be excluded as contaminations. The work of Ross,¹ Beeler and Helmholz,² Kleinschmidt,³ and others substantiates this view. Recently the entire question was reopened by Langer and Soldin⁴ who claim that all former work in which liquid mediums had not been used for the isolation of bacteria is open to criticism. In a series of 138 cases they isolated *Streptococcus lacticus* 128 times, *Bacillus coli* sixteen times, and *Bacillus lactis aerogenes* four times; *Bacillus coli* was associated with *Streptococcus lacticus* six times. Occasionally, a single examination revealed sterile urine, but on repetition bacteria were found. At that no account is taken of anaerobic bacteria.

Langer and Soldin speak only of washing the urethra thoroughly with a 10 per cent. boric acid solution. The solvent for the boric acid is not mentioned, and in a single sentence, without any citation of experiments, they consider all portions of the urine alike with regard to bacterial content and formed elements. The most striking features of their series are the constant presence of bacteria of the colon group and the complete absence of staphylococci which are normally present in the female urethra. This is in direct contrast to the findings of Beeler and Helmholz,² namely, that only exceptionally were bacilli of the colon group found, and when organisms were present they were usually staphylococci or diphtheroids. Kleinschmidt cultured, on solid

* Received for publication Dec. 26, 1921.

* From The Children's Memorial Hospital, Laboratory of The Otho S. A. Sprague Memorial Institute and the Section of Pediatrics, Mayo Clinic.

1. Ross, A.: The Bacteriology of the Urinary Tract in Children, *Lancet* **1**:654, 1915.

2. Beeler, C. and Helmholz, H. F.: The Bacteriology of the Urine in Healthy Children and Those Suffering from Extra-urinary Infections, *Am. J. Dis Child.* **12**:345 (Oct.) 1916.

3. Kleinschmidt, H.: Zur Bakteriologie des Harns beim Säugling, *Jahrb. f. Kinderh.* **94**:77, 1921.

4. Langer, H. and Soldin, M.: Zur Aetiologie der Säuglingspyelitis, *Ztschr. f. Kinderh.* **19**:161, 1919.

mediums, fifty-four specimens of urine from female patients and obtained sterile urine in all but ten, while in liquid mediums he obtained bacteria in thirty-two of sixty-two cultures. Further, he says that he was rarely able to obtain the same flora in successive examinations, which he interprets as the result of varying contaminations. Dextrose bouillon yielded positive cultures more often than plain bouillon; the percentages, however, are not indicated. He isolated *Streptococcus lacticus* more often than any other organism; second in line are members of the colon group, third the staphylococci.

Inasmuch as the former work of one of us was carried on entirely on various solid mediums, it was thought wise to repeat the work, using also the liquid culture medium suggested by Langer and Soldin. This

TABLE 1.—RESULTS OF CULTURES

No.	Sex	Specimen 1		Specimen 2	
		Liquid Medium	Solid Medium	Liquid Medium	Solid Medium
19	Boy	<i>Bacillus subtilis</i>	Negative	Negative.....	Negative
28	Girl	Negative.....	Negative	<i>Staphylococcus</i>	Negative
30	Boy	Negative.....	Negative	Gram-positive bacillus spore-former	Negative
31	Girl	Gram-negative streptococcus not identified	Negative	Negative.....	Negative
40	Boy	Gram-positive spore-former	Negative	Negative.....	Negative
80	Girl	Gram-positive diplococcus not <i>Streptococcus lacticus</i>	Negative	Negative.....	Negative
10*	Boy	Gram-positive staphylococcus after one week	Negative		
32*	Girl	Gram-negative bacillus short, <i>Bacillus subtilis</i>	Negative		
33*	Boy	<i>Staphylococcus</i>	Negative		
34*	Boy	<i>Bacillus subtilis</i>	Negative		
77*	Boy	Gram-positive staphylococcus	Negative		

* One specimen only was obtained.

seemed the more important as the constant presence of *Streptococcus lacticus* in the normal urine would be of great importance in settling the problem of the mode of infection in pyelitis.

The infants from whom the urine was taken for this study ranged in age from 6 weeks to 16 months. All had normal temperatures and were normal or nearly normal in weight. All were free from any infection or disease, as indicated by physical examination. Some of the infants were entirely breast fed, others were breast and bottle fed, and still others were fed entirely with artificial food.

The technic of obtaining urine was practically the same as that described by Beeler and Helmholtz. The catheters used were of metal, varying from 1.5 to 2.5 mm. in diameter, with a short rubber tube attached by means of which the flow of urine could be controlled and collected in two separate tubes. The catheters were sterilized indi-

vidually in large test tubes, so that they could be removed without danger of contamination.

To catheterize a patient three persons were always at hand; one to hold the limbs of the child, one to separate the labia, cleanse the parts, and pass the catheter, and a third to play the stream of compound solution of cresol, pass out the catheter, and hold the test tubes to receive the urine.

The meatus was cleansed as follows: The labia were held apart or the foreskin was retracted and the debris loosened by a small sterile applicator, while a steady stream of 1 per cent. compound solution of

TABLE 2.—RESULTS OF CULTURES

No.	Sex	Specimen 1			Specimen 2		
		Liquid Medium	Solid Medium	Colonies in Each C.c.	Liquid Medium	Solid Medium	Colonies in Each C.c.
12	Girl	Negative.....	Negative.....	0	Staphylococcus	Staphylococcus	1,000
19	Boy	Bacillus subtilis	Negative.....	0	Negative.....	Negative.....	0
26	Boy	Negative.....	Negative.....	0	Bacillus subtilis	Bacillus subtilis	Countless
28	Girl	Negative.....	Negative.....	0	Staphylococcus	Negative.....	0
30	Boy	Negative.....	Negative.....	0	Gram-positive bacillus, spore-former	Negative.....	0
31	Girl	Streptococcus, not identified	Negative.....	0	Negative.....	Negative.....	0
40	Boy	Gram-positive bacillus, spore-former	Negative.....	0	Negative.....	Negative.....	0
48	Boy	Staphylococcus	Staphylococcus	1	Negative.....	Negative.....	0
78	Boy	Gram-positive staphylococcus and non-pathogenic bacillus	Gram-positive staphylococcus and non-pathogenic bacillus	4	Negative.....	Negative.....	0
80	Girl	Gram-positive diplococcus not <i>S. lacticus</i>	Negative.....	...	Negative.....	Negative.....	0

cresol was played on the region of the meatus. A dry sterile applicator was then applied directly over the meatus to remove any excess fluid. The catheter was then inserted. If there was enough urine in the bladder two specimens were collected.

The urine was cultured in tubes containing 1 per cent. dextrose broth titrated to a hydrogen ion concentration of from 7.6 to 7.8 on plates of litmus-lactose-agar, made by adding 1 per cent. agar, 1 per cent. lactose and 1 per cent. litmus to plain broth that had been titrated to p_H 7.6-7.8. About 1 c.c. of urine was used in about 8 c.c. of broth, and from 0.5 to 1 c.c. for the plating in litmus-lactose-agar. The number of colonies of bacteria indicated in Tables 2 and 3 represent the number of bacteria for each cubic centimeter of urine. All streptococci were subcultured in litmus milk for identification. *Streptococcus*

lacticus was identified by a method very kindly furnished us by Prof. E. G. Hastings of the University of Wisconsin. The identification is based on the fact that *Streptococcus lacticus* reduces the litmus before curdling the milk, and the other streptococci produce a pink curd in the milk without reducing the litmus.

Seventy infants, thirty-five girls and thirty-five boys, were studied. The findings can best be grouped under headings as follows:

1. *All Cultures Negative*.—In this group there were thirty infants, seventeen girls and thirteen boys. In only twenty-one of the thirty was it possible to obtain enough urine for two specimens. This group represents 40 per cent. of the samples examined and in two-thirds of these the sterility of the urine was determined in duplicate on Specimens 1 and 2. The cultures in cases in which two specimens were obtained are included in this group only when all four were sterile. In the others of this series one specimen only was obtained, and cultures were sterile in both liquid and solid mediums.

2. *Cultures in Solid Mediums Negative, in Liquid Mediums Positive*.—Much to our surprise, this group was relatively small, eleven cases (five girls and six boys). Langer and Soldin's work led us to believe that this would make up the largest group of the series. The various organisms in cultured liquid mediums are given in Table 1. The importance of this group is paramount in disproving Langer and Soldin's contention that liquid mediums are essential for this work. In only 15 per cent. has it made a difference, and even here the significance is doubtful.

3. *Cultures in Solid Mediums Positive, in Liquid Mediums Negative*.—Of the three cases in this group (two boys and one girl), contamination was unquestionable in two; in the third were two colonies of streptococci, which may or may not have been due to contamination.

4. *Cultures of One Specimen Positive, and All Cultures from the Other Specimen Negative*.—Specimens 1 and 2 refer to the first and second portions of urine obtained by catheterization. There were ten cases in the group (six boys and four girls, Table 2). Contrary to expectation Specimen 1 was sterile four times and Specimen 2 showed growth six times, indicating that the first portion of the urine voided does not necessarily contain the contaminating bacteria. In only two of the four was there growth in the solid mediums inoculated from Specimen 2.

5. *All Cultures Positive*.—In most of the twenty-six cases in this group (fourteen boys and twelve girls), all the cultures showed growth although occasionally one or another was negative. The num-

TABLE 3.—RESULTS OF CULTURES

No.	Sex	Specimen 1			Specimen 2		
		Liquid Medium	Solid Medium	Colonies in Each C.c.	Liquid Medium	Solid Medium	Colonies in Each C.c.
2	Girl	Negative.....	Negative.....	0	Gram-positive staphylococcus, large	Gram-positive staphylococcus, large	1,000
5	Girl	Gram-positive streptococcus not identified	Gram-positive staphylococcus, large	920			
6	Girl	Gram-positive streptococcus not identified, gram-negative bacillus non-pathogenic	Gram-negative streptococcus not identified, gram-negative bacillus, gram-negative staphylococcus	570			
8	Girl	Gram-negative bacillus probably B. coli, gram positive streptococcus not identified	Gram-negative bacillus probably B. coli	800			
22	Boy	Gram-positive streptococcus and Streptococcus lacticus	Bacillus coli	130	Gram-positive streptococcus and Streptococcus lacticus		
25	Boy	Gram-positive staphylococcus, large	Gram-positive staphylococcus, large	6			
36	Boy	Staphylococcus	Staphylococcus	Staphylococcus	38
37	Boy	Staphylococcus, large	Staphylococcus, large	2	Staphylococcus, large	Staphylococcus, large	26
42	Girl	Gram-positive staphylococcus, large, and S. lacticus	Staphylococcus and B. subtilis	20	Gram-positive staphylococcus, large, and S. lacticus	Staphylococcus, B. subtilis, and one colony of S. lacticus	8
44	Girl	Streptococcus, not S. lacticus	Streptococcus, not S. lacticus	Few
45	Girl	Streptococcus lacticus and diplococcus	Streptococcus lacticus and diplococcus	Streptococcus lacticus and diplococcus	6
47	Girl	Gram-positive staphylococcus	Gram-positive staphylococcus	2	Gram-positive staphylococcus	Negative.....	0
48	Boy	Gram-positive staphylococcus	Gram-positive staphylococcus	1	Negative.....	Negative.....	0
53	Girl	Gram-negative bacillus not B. coli and gram-positive staphylococcus	Gram-negative bacillus not B. coli	2			
54	Boy	Gram-positive staphylococcus, large	Staphylococcus, large	58	Few staphylococci, large	Negative.....	0
56	Boy	Gram-negative staphylococcus	Staphylococcus	100	Staphylococcus	Staphylococcus	100
59	Boy	Staphylococcus, large	Staphylococcus, large	Staphylococcus, large	50
60	Boy	Gram-positive staphylococcus, large	Staphylococcus, large	6	Streptococcus, not S. lacticus		
61	Boy	Staphylococcus, large	Staphylococcus, large	15	Staphylococcus, large		
64	Girl	Streptococcus lacticus and gram-negative spore-former	Staphylococcus, large and Streptococcus lacticus	3			
67	Boy	Gram-negative staphylococcus	Bacillus subtilis	1			

TABLE 3.—RESULTS OF CULTURES—(Continued)

No.	Sex	Specimen 1			Specimen 2		
		Liquid Medium	Solid Medium	Colonies in Each C.c.	Liquid Medium	Solid Medium	Colonies in Each C.c.
74	Girl	Staphylococcus, large and spore-forming bacillus	Staphylococcus, large and spore-forming bacillus	3	Staphylococcus, large		
75	Boy	Staphylococcus, large	Spore forming bacillus	10	Spore-forming bacillus		
76	Boy	Gram-negative bacillus, non-pathogenic	Gram-negative bacillus, non-pathogenic	2	Gram-negative bacillus, non-pathogenic	Negative.....	0
81	Boy	Negative.....	Bacillus coli and Streptococcus lacticus	4	Streptococcus lacticus and Bacillus coli	Streptococcus lacticus and Bacillus coli	200
82	Boy	Negative.....	Staphylococcus, large	1	Gram-negative bacillus, spore-former	Negative.....	0
83	Girl	Staphylococcus, large	Staphylococcus, large	10	Staphylococcus, large, and streptococcus not identified	Staphylococcus, large	6
85	Girl	Two streptococci, one S. lacticus	Negative.....	0	Two streptococci, one S. lacticus	Two streptococci, one S. lacticus	Many

ber of bacteria for each cubic centimeter is of interest in that in only six cases were there 100 or more organisms for each cubic centimeter of urine. In eight cases there were from ten to 100 organisms for each cubic centimeter, and in twelve there were less than ten. In Table 3 the results of the cultures in this group are given in detail.

In fourteen instances streptococci were isolated from the urine; in six the organism was definitely identified as the *Streptococcus lacticus*, in five it was not definitely identified, and in three it was definitely not *Streptococcus lacticus*. Thus of seventy specimens of urine *Streptococcus lacticus* was possibly present in eleven, and definitely absent in fifty-nine (84.28 per cent).

DISCUSSION

The results of our studies emphasize again the futility of obtaining evidence by the method of Langer and Soldin that in any way will help to settle the problem of the mode of infection in pyelitis. The error that creeps in by contamination, even when all precautions are taken, is such that the evidence obtained is always open to criticism. Our data show that in three-sevenths of the specimens examined the urine was sterile; in two-thirds of these the determination was made in duplicate. We cannot agree with Kleinschmidt that at each catheterization a different flora is obtained, nor with Langer and Soldin that a sterile specimen is only an accident, and repeated catheterization will always yield

bacteria in the urine. We have recatheterized repeatedly and obtained identical results both with regard to sterility and flora. Furthermore, we wish to call attention to types of organisms constantly found by Kleinschmidt and by Langer and Soldin, namely, those of the colon group and *Streptococcus lacticus*, all inhabitants of the intestinal canal and so far as we know not present normally in the urethra. Kleinschmidt asserts that by taking smears from the meatus after cleansing it he was able to prove the constant presence of an organism of the same type as that found in his cultures of the urine. The method used by Langer and Soldin of obtaining cultures is also open to criticism since by washing out the urethra, organisms may easily be washed into the bladder. Langer and Soldin found long chains of streptococci, as shown in one of their illustrations. These they believe have grown from organisms coming from the kidney. The more plausible interpretation is that they are washed in from the urethral opening and are essentially contaminations, as it is not likely that organisms would grow so rapidly in the urine and not grow in more favorable culture mediums after inoculation. Our findings are further at variance with those of Kleinschmidt and of Langer and Soldin in the frequency of occurrence of the *Streptococcus lacticus*, which was almost omnipresent in their cultures. The *Streptococcus lacticus* was definitely identified in only six instances, it may have been present in five others, so that at most it was present in 15 per cent. of the urines examined. In six of eleven instances the *Streptococcus lacticus* was found in the liquid medium and not recovered on the solid medium.

CONCLUSIONS

1. The urine of infants is sterile on culture in from one-third to one-half of the experiments.
2. *Streptococcus lacticus* is only exceptionally found in the urine of infants.
3. The chances of contamination are so great that the presence of organisms in the urine does not prove, without further control, that they have come from the kidney.

THE VALUE OF CUTANEOUS SENSITIZATION TESTS EMPLOYED IN ECZEMA AND PAPULAR URTICARIA OF CHILDHOOD*

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In this discussion, we are not concerned with the controversy as to whether the cutaneous sensitization observed clinically in eczema, urticaria papulosa and angioneurotic edema in infants and children is a phenomenon of anaphylaxis or a state of allergy. We believe that the question will be settled when the mechanism of protein sensitization is more definitely known. However, the fact remains that local cutaneous reactions are brought to light when various proteins are applied by cutaneous or intracutaneous tests to the skin of patients who are subjects of the diseases mentioned. The results indicate that these cutaneous reactions depend on a protein substance which is the essential cause of the efflorescence in a comparatively large number of cases. Moreover, the cause of the disease having been determined, with intelligent cooperation on the part of the parents of the patient in regard to diet, the clinical cure far surpasses the results of any other mode of treatment.

The application of cutaneous sensitization tests in cases of dermatitis in adults in which a protein may be suspected as a possible cause has been a routine practice of late in the Dermatological Dispensary of the Jefferson Medical College Hospital. The favorable results derived from the practice prompted us to apply protein sensitization tests to children having eczema and urticaria.

Pirquet¹ was the first to suggest a method for determining cutaneous sensitization to proteins, but it remained for Schloss to make clinical application of the procedure in children. Schloss'² patient was a boy, 8 years of age, who was subject to marked urticarial lesions caused by the ingestion of eggs, oatmeal and almonds. The patient's history suggested that the urticaria subsequent to the ingestion of these foods was not a congenital condition but was acquired during early life. It was found that the cutaneous reaction was produced only by the protein constituent of egg, almonds and oats. During the time the

* Received for publication Nov. 21, 1921.

* From the Department of Dermatology, Jefferson Medical College.

1. Pirquet, C.: *Arch. Int. Med.* **7**:259 (March) 1911.

2. Schloss, O. M.: *Am. J. Dis. Child.* **3**:341 (May) 1912.

patient was on a diet free from these substances, he was also free from urticarial attacks. Schloss succeeded eventually in immunizing this boy by feeding him gradually increasing doses of the protein constituent of eggs. Blackfan³ found evidence of susceptibility to protein in twenty-two out of twenty-seven patients with eczema whom he tested intracutaneously. When his patients were placed on a diet free from or limited in animal proteins, the eczema was markedly improved in each case. Engman and Wander⁴ found that in their series 78 per cent. of children with eczema are sensitized to some protein. In the cases in which the patients' parents cooperated with them, the results were "brilliant." In our own series, the percentage of positive sensitization and the general results compare favorably with those of Blackfan, Engman and Wander.

From our own work on adults, we found that the intracutaneous method is more sensitive and subject to fewer errors than the cutaneous method. It is not possible to make a series of abrasions that exactly correspond in length and depth. It is impossible to apply the same amount of powdered protein substance to the abrasion, unless previously weighed—an almost impossible and certainly impractical undertaking, especially when one is called on to make a large number of tests. On the other hand, when the intracutaneous method is employed, the solution containing the protein can be standardized. The standardization depends on the percentage of nitrogen in each protein determined by the Kjeldahl method. Having standardized the solution, the exact amount to be injected can be measured out by an accurate syringe. In our investigation we employed the commercial product throughout. We had occasion to compare the end-results of tests with the commercial proteins with those performed with a number of protein substances that we ourselves had prepared according to the method of Wodehouse and Olmstead.⁵ The results were found to be identical.

The protein test substance is dissolved in physiologic solution of sodium chlorid and the usual amount of phenol was added as a preservative. The solution is then tested for sterility. The skin of the arm is cleansed, and 0.05 c.c. of the desired test protein is injected intracutaneously. A successful injection is followed immediately by the appearance at the site of the injection of a raised white spot resembling a wheal. More than one control, consisting of the menstrum, is used.

The cutaneous reaction may be immediate or delayed for forty-eight hours. The appearances necessary to establish a positive immediate

3. Blackfan, K. D.: *Am. J. Dis. Child.* **11**:441, 1916.

4. Engman, M., Jr., and Wander, W. G.: *Arch. Dermat. & Syph.* **3**:223 (March) 1921.

5. Wodehouse, R. P., and Olmstead, J. M. D.: *Boston M. & S. J.* **176**:467, 1917, *ibid.* **177**:85, 1917.

test are a wheal and a red areola surrounding the wheal. The criteria for a delayed positive test are a papular induration and an erythema persisting for forty-eight hours. The intensity of the reaction is determined by reading the tests against the controls. If the wheal or papule equals the control and presents no erythema, it is negative; if it is half again as large and surrounded by erythema, it is +; if twice as large, it is ++, and so on.

Twenty-three infants and children with eczema were tested. Eight, or 35 per cent., gave negative reactions. Fifteen, or 65 per cent., had one or more positive reactions. Six, or 40 per cent., of the fifteen patients were clinically cured; three patients, or 20 per cent., showed marked improvement; six, or 40 per cent., were improved.

Twelve children with papular urticaria were tested. Three, or 25 per cent., were negative as far as reactions were concerned. Nine, or 75 per cent., reacted to one or more proteins. Three of the nine cases were clinically cured; four were markedly improved. Of the two remaining children, one reacted to strawberry +, orange +, and banana +; the other one reacted to potatoes + and tomatoes +. Both children failed to improve on a restricted diet.

The cause and progress in several of the cases in our series are worthy of more detailed comment.

SUMMARY OF CASES

CASE 1 (Table 1).—H. S., aged 3 months, breast fed, had an eczema of the face. The child reacted to mother's milk +, cows' milk +. Elimination of the mother's and of the cows' milk failed to cure or improve the dermatosis.

CASE 2 (Case 4, Table 1).—M. K., aged 14 months, had an eczema of the face. The reaction to food proteins was positive for egg yolk, ++; egg white, ++, and oatmeal +. The patient was placed on a diet free from eggs and cereals, and during the first two weeks colonic irrigations were ordered. When last observed the eczema was very much improved.

CASE 3 (Case 8, Table 1).—H. L., aged 8 months, had had an eczema of the face for four months when first examined. He reacted to rice, ++, and barley, ++. He was given colonic irrigations of physiologic solution of sodium chlorid and a diet consisting of milk. After the eczema had been clinically cured, the patient was tested and again reacted to barley and rice.

CASE 4 (Case 12, Table 1).—J. C., aged 4 years, had a generalized papulovesicular eczema of two months' duration. The reaction to food proteins was positive for beef, +++; lamb, ++, and peanuts, +. The elimination of all forms of meat from the diet resulted in a clinical cure.

CASE 5 (Case 5, Table 1).—This case serves as an illustration of how difficult it is at times to prove the pathogenesis of a suspected cause. P. S., aged 11 months, had an eczema of the face and an abscess of the left cheek. The reaction to food proteins was negative, but the response to the *Staphylococcus pyogenes* was ++. Surgical attention was first given the abscess. As it improved it was noticed that the eczema was improving. By the time the abscess had nearly healed, the eczema was practically well. When the patient was last seen the eczema had completely cleared up. The patient failed to react to food proteins but reacted to bacterial proteins. The eczema first

TABLE 1.—PROTEIN REACTION IN CASES OF ECZEMA; RESULTS OF TREATMENT

Case	Age	Distribution	Duration	Reaction	Result
1. H. S.	3 mos.	Face	1 mo	Mother's milk + Cows' milk +	No improvement
2. E. H.	10 mos.	Face	1 mo.	Potatoes ++ Herring ++	Improved
3. F. W. C. ...	3 yrs.	General	6 mos.	None	Unimproved
4. M. K.	14 mos.	Face	2 mos.	Egg yolk ++ Egg whites ++ Oatmeal +	Marked improvement
5. P. S.*.....	11 mos.	Face	2 wks.	Staphylococcus pyogenes ++	Clinical cure
6. M. S.	12 yrs.	Upper and lower extremities	11 mos.	None	Unimproved
7. S. G.	14 mos.	Lower ex- tremities	2 mos.	None	Unimproved
8. H. L.	8 mos.	Face	4 mos.	Barley ++ Rice ++	Clinically cured
9. R. M.	16 mos.	Face	5 wks.	Rye + Egg yolk ++ Egg white ++	Clinically cured
10. M. E. T. ...	8 mos.	Face	2 wks.	Tuberculin ++++	Not improved
11. W. McK. ...	2 yrs.	General	21 mos.	Cheese +	Not improved
12. J. G.	4 yrs.	General	2 mos.	Beef +++ Lamb ++ Peanuts +	Clinically cured
13. N. P.	3 yrs.	General	21 mos.	Spinach ++	Improved markedly
14. G. M.	2 yrs.	Face	6 mos.	Egg white ++ Wheat ++	Improved
15. P. R.	19 mos.	Face	2 wks.	Oatmeal +++	Clinically cured
16. L. R.	3 yrs.	Upper ex- tremities	4 wks.	Tomatoes +++	Clinically cured
17. J. R.	8 mos.	Upper ex- tremities	4 mos.	None	Not improved
18. B. B.	14 mos.	Lower ex- tremities	2 mos.	Wheat +++ Egg white ++ Potato + Rice +	Improved
19. W. T.	4 yrs.	General	1 yr.	Pork +++ Beef +++ Veal ++	Marked improvement
20. E. B.	2 yrs.	Face	2 wks.	Cheese + Beans ++ Coffee +	Improved
21. L. Z.	4 yrs.	Face	7 wks.	Tomatoes ++ Grape fruit ++ Peas ++	Improved
22. R. H.	5 yrs.	General	2 yrs.	Cod fish ++ String beans + Lima beans +	Improved
23. C. R.	2 yrs.	Face and hands	6 mos.	Milk + Veal +	Not improved

* This patient also had an abscess.

improved and later cleared up entirely following the surgical treatment of the abscess. Apparently the cause of the eczema in this case was a bacterial protein.

CASE 6 (Case 2, Table 2).—S. E., aged 6, had an urticarial eruption of three days duration. All sensitization tests were negative with the exception of cucumber ++. Treatment consisted of colonic irrigation and an antipruritic lotion locally. The patient has been under observation for six months without a recurrence of urticarial lesions.

CASE 7 (Case 6, Table 2).—W. S., aged 3 years (a private patient) had a papular urticaria involving the face and extremities. Herring gave a ++ reaction. The tests were made following the second attack, when it was found that herring was responsible. The mother of the patient volunteered the information that the child had been given anchovies thirty-six hours before the last attack, and that the patient had had anchovies for the first time in May, 1921. The third attack was brought about deliberately.

TABLE 2.—PROTEIN REACTION IN CASES OF PAPULAR URTICARIA; RESULTS OF TREATMENT

Case	Age	Distribution	Duration	Reaction	Result
1. J. H.	7 yrs.	Upper and lower extremities	2 yrs.	Negative	Unimproved
2. S. E.	6 yrs.	Upper and lower extremities	3 days	Cucumber ++	Clinically cured
3. C. H.	18 mos.	Upper and lower extremities	6 mos.	Oats ++ Veal ++	Improved
4. S. K.	3 yrs.	General	10 days	Chicken ++++	Clinically cured
5. G. P.	7 yrs.	General	2 yrs.	Strawberry + Orange + Banana +	Not improved
6. W. S.	3 yrs.	Upper and lower extremities and face	5 mos.	Herring ++	Clinically cured
7. J. H.	7 yrs.	General	18 mos.	Beef ++ Egg yolk +++ Egg white +++ Oats ++	Much improved
8. W. T.	3 yrs.	Upper and lower extremities	1 yr.	Milk +++	Improved
9. I. G.	4 yrs.	Upper and lower extremities	1 yr.	Potato + Cows' milk ++ Egg white +++ Wheat +++	Improved
10. I. G.	18 mos.	Extremities	1 mo.	Negative	No improvement
11. E. M.	2 yrs.	Face	2 mos.	Negative	No improvement
12. L. P.	3 yrs.	Lower extremities	1 yr.	Potatoes + Tomatoes +	No improvement

CASE 8 (Case 8, Table 2).—W. T., aged 3 years, was affected with papular urticaria of one year's duration. A positive reaction to a food protein was obtained with milk +++. Colonic irrigations, alkalis and phenyl salicylate by mouth and elimination of all dairy products from the diet gave an excellent result. At the end of nine days the patient was free from urticarial lesions. Three days later his mother gave him ice cream and the urticaria reappeared the same day.

CASE 9 (Case 9, Table 2).—I. G., aged 4 years, has had a generalized urticarial eruption for the past twelve months. The reaction to food proteins

was: beef ++, egg yolk ++, egg white ++, wheat +++. That the urticaria was only improved, we believe, is due to the fact that the cooperation on the part of the mother in regard to diet was not entirely satisfactory.

Reaction to more than one protein in the same patient is a common occurrence. Reactions to test proteins which apparently have not entered into the diet of the patient have also been recorded. Also nonprotein substances, such as apothecin, quinin⁶ and procain⁷ have been found to cause skin reactions. The explanation of these apparent inconsistencies is to be found in the work of Schloss,² Wells and Osborne.⁸ Schloss has pointed out the importance of recognizing that many foods are biologically related. Wells and Osborne, from their extensive investigations, concluded that the chemical structure rather than the biologic origin of the proteins determines the specificity of the anaphylactic reaction. How nonprotein substances operate to cause skin reactions has not been answered as yet. It has been suggested that chemicals like arsenic, quinin and other substances form compounds and alter the proteins of the body in a manner so as to form foreign proteins. Experimental evidence is lacking.

A factor that precludes a greater number of clinical cures in infants and children with eczema and papular urticaria associated with positive reactions to proteins, is the condition of the gastro-intestinal tract of these patients. Lack of unanimity exists among investigators in regard to permeability of undigested proteins when the alimentary epithelium is intact, but all agree that anatomic or functional abnormalities of the gastro-intestinal tract permit unaltered proteins to pass into the blood stream through the gastro-intestinal wall. Schloss and Worthen⁹ found, by applying the precipitin test to the urine in atrophic infants with gastro-intestinal disorder, that unaltered proteins were absorbed through the walls of the intestine. Lust,¹⁰ Modeglioni and Benini¹¹ found that nutritional disorders favor the absorption of undigested proteins in children. Myehof and Pribam¹² found that enteritis increases the permeability of the intestinal wall to crystalloids and colloids. Barnathan¹³ states that disturbances in the gastro-intestinal tract interfering with the proper function of the digestive enzymes favor alimentary sensitization.

6. Mook, W. H.: *Arch. Dermat. & Syph.* **1**:651 (June) 1920.

7. Lane, C. G.: *Arch. Dermat. & Syph.* **3**:235 (March) 1921.

8. Wells, H. G., and Osborne, O. T.: *J. Infect. Dis.* **12**:341, 1913.

9. Schloss, O. M., and Worthen, T. W.: *Am. J. Dis. Child.* **11**:342 (May) 1916.

10. Lust: *Jahrb. f. Kinderh.* **77**:244 and 283, 1913.

11. Modeglioni, E., and Benini, R.: *Policlinico* **21**:540 (Dec. 20) 1914; *Abst. J. A. M. A.* **64**:476 (Jan. 30) 1915.

12. Myehof and Pribam, E.: *Wien. klin. Wchnschr.* **22**:875, 1909.

13. Barnathan: Quoted by Highman, W. G., and Michael, J. C.: *Arch. Dermat. & Syph.* **2**:531 (Nov.) 1920.

From the preceding it may be inferred that proteins biologically related or chemically similar to an offending protein, though the latter may have been omitted from the patient's diet, may continue to cause the dermatosis. The condition of the gastro-intestinal tract may favor or inhibit the absorption of unaltered proteins to which the patient is sensitized and thereby either preclude the possibility of a clinical cure or help to increase the number of clinical cures.

SUMMARY

1. We have limited ourselves to the value of protein sensitization tests in children with eczema and papular urticaria.

2. The protein sensitization test proved of considerable value in ascertaining the etiologic factor in a fair number of cases of eczema and papular urticaria.

3. The elimination of specific offending proteins will not affect a cure in all cases of eczema or urticaria in children.

4. To be of value the food test must be ++ or greater.

5. We may assume, that by correcting the gastro-intestinal abnormalities, an increase in the number of clinical cures is certain of attainment.

STUDIES OF INFANT FEEDING. XVII. A BACTERIO-
CHEMICAL STUDY OF THE ACID STOOLS EXCRETED
BY BREAST-FED AND BOTTLE-FED INFANTS *

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It has been our experience to find that the stools from all babies receiving breast milk give an acid or neutral reaction when tested with litmus and that the stools from bottle-fed babies receiving simple cow's milk mixtures may be acid, neutral or alkaline when so tested. It has also been our experience to note that excoriation of the buttocks may often be associated with the elimination of acid stools.

The cause of the acid stools from bottle-fed babies has been a question of much theory and conjecture and up to the present time has not received any satisfactory explanation. It is our belief that the reaction of the stools may be dependent, to a great extent, on the chemical composition of the food ingested; that the composition of the food influences the bacterial growth within the intestines and determines the predominance of bacterial types; and that the type of bacteria present may account for the nature of some of the substances found in the feces.

This investigation was undertaken in order to learn something about the nature and cause of the acid stools eliminated by infants and involves both bacteriologic and chemical examinations of such stools. In this connection we have made determinations of the water soluble acidity and the total volatile acid content of twenty-four hour amounts of feces, the feces being marked by the use of carmine red. The nature of the volatile acid has also been investigated.

When this investigation was started we adopted the customary procedure of steam distillation for separating the volatile soluble fatty acids from the feces. We acidified with sulphuric acid and did not carefully control the volume of liquid in the distilling flask. We generally allowed the contents of the flask to concentrate as the distillation proceeded. This method was satisfactory in much of our work, especially on bacterial growths where little organic matter other

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* This investigation was conducted in the Boston Floating Hospital Laboratories.

than the fatty acids was present. It was customary to distill until a distillate neutral to litmus was given off.

When we began distilling stools from breast fed babies we noticed that the distillation continued to yield an acid distillate for a much longer period than had the previous materials. We concluded that the sulphuric acid must be decomposing some of the organic matter present, yielding volatile fatty acids, and thus prolonging the distillation indefinitely. To eliminate this possibility we so modified our technic as to eliminate all insoluble material from the distilling flask, and we acidified the material with phosphoric acid instead of sulphuric acid. This materially improved the method, but the distillate still continued acid for a greater volume than we had noticed before. Finally, we decided to investigate the nature of the fatty acids and we adopted the general method described by Dyer.¹ The large volume necessary to drive over all the fatty acids indicated the presence of formic acid. This observation was confirmed by qualitative tests. It became apparent that in the stools from breast fed babies we were for the first time encountering formic acid.

Dyer has shown that the distillation of volatile fatty acids at constant volume proceeds with a certain regularity and that the titration figures, when plotted as percentages on logarithmic coordinate paper, give a straight line for any individual fatty acid, and for a mixture of fatty acids a curve of variable shape, depending upon the particular fatty acids present in the mixture. By distilling pure acids in the apparatus used, the standard lines for these individual acids may be plotted as guides in the examination of mixtures. In order to determine the nature of the fatty acids in an unknown mixture we plotted the curve obtained from the distillation and compared this with the standard curves for pure acids.

As our study of the acid stools progressed we noted that the volatile acids we were dealing with were acetic and formic acids. We have therefore obtained the distillation figures and plotted the curves for pure acetic acid, pure formic acid and a mixture of equimolecular parts of the two acids. These distillation figures are given in Table 1 and the curves obtained are shown in Figure 1.

In plotting our curves we found that in every case our lines curved slightly to the left at the higher values. Dyer found that pure individual acids gave straight lines. The reason for this slight deviation was that our technic had for convenience been standardized with an assumed total titration rather than by carrying the titration to the true limit; that is, we distilled until the titration value of the 100 c.c. portion was less than 0.2 c.c. of tenth normal alkali. The sum of all titrations to this point was called the total titration. Since we were distilling a mixture of fatty acids we could not use Dyer's formula

1. Dyer: *J. Biol. Chem.* **28**:468, 1917.

TABLE 1.—COMPARISON OF RATES OF DISTILLATION OF ACETIC ACID, FORMIC ACID AND AN EQUIMOLECULAR MIXTURE OF THE TWO ACIDS

Volume Distilled	Percentages Titrated		
	Acetic Acid	Acetic-Formic Mixture	Formic Acid
100.....	29.55	25.24	19.37
200.....	50.30	43.97	35.48
300.....	64.65	57.94	48.35
400.....	74.74	68.08	58.65
500.....	81.95	75.00	66.94
600.....	87.00	81.25	73.52
700.....	90.57	85.65	78.86
800.....	93.13	88.96	83.12
900.....	95.02	91.56	86.55
1000.....	96.37	93.57	89.30
1100.....	97.40	95.12	91.45
1200.....	98.07	96.36	93.17
1300.....	98.63	97.30	94.57
1400.....	99.00	98.00	95.70
1500.....	99.34	98.51	96.68
1600.....	99.63	98.92	97.50
1700.....	99.90	99.30	98.06
1800.....	100.00	99.60	98.57
1900.....	99.93	98.97
2000.....	100.00	99.34
2100.....	99.60
2200.....	99.84
2300.....	100.00

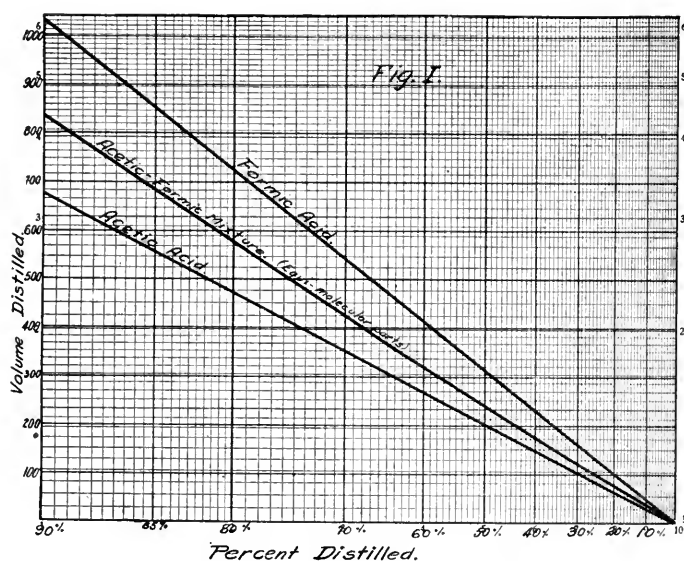


Fig. 1.—Distillation curves for acetic acid, formic acid and an equimolecular mixture of acetic and formic acids.

for computing the total titration, and since the error introduced by using our assumed total value did not materially change the shape of the curve in its lower portion, we preferred to use our method rather than to introduce elaborations which did not bid fair to increase materially the accuracy of our conclusions.

The angle of inclination of the curve is a function of the particular fatty acid present, the slope decreasing as the fatty acids become higher in the series. The rate at which the acid distilled off increases with the higher fatty acids; thus caproic acid distills off completely in 400 c.c., whereas acetic acid requires 2,500 c.c. and formic acid 4,200 c.c. to drive over the last trace of the acid.¹

The effect of these characteristics on the curve for a mixture of fatty acids is that the curve starts with a gradual slope as the higher fatty acids are driven off, and the slope of the curve increases when the lower fatty acids predominate. Ultimately the curve should parallel that of the lowest fatty acid present in the mixture, provided the distillation is conducted far enough.

It is evident that the curve for a mixture cannot rise more abruptly than does the curve for the lowest individual fatty acid present. Our results with the stools from breast-fed babies have consistently produced lines rising between the curves for acetic acid and formic acids, proving conclusively that formic acid must be present in the mixture, and in considerable amount. In contrast with this, we found that the curves obtained from stools from babies receiving modified milk formulae had less slope than the acetic acid curve and did not cross it.

The difference between the two types is quite evident from the distillation figures, for the stools from breast-fed babies required a distillation of from 1,300 to 1,700 c.c.; whereas the end point on babies receiving modified milk formulae was reached with a smaller volume of distillate. An example of the titration figures for each class is given in Table 3.

1. METHODS

Suspension of Stool in Distilled Water.—Place a twenty-four hour quantity of feces in a 500 c.c. volumetric flask and add distilled water to fill to the mark and then add 2 c.c. of chloroform. After shaking to disintegrate the larger lumps, allow the flask to stand, with occasional shaking for two hours.

Water Soluble Acidity.—Remove about 75 c.c. of the above suspension and centrifugalize. Pipette 50 c.c. of the clear liquid into an Erlenmeyer flask, add a few drops of phenolphthalein solution and titrate with tenth normal alkali. Express results as cubic centimeters of tenth normal alkali per twenty-four hours of feces.

Volatile Acid.—Shake the suspension of the stool in water and measure off 400 c.c. into a graduated cylinder. Transfer this to a 500 c.c. volumetric flask, washing the sides of the cylinder with a little distilled water. Add 0.5 c.c. of phenolphthalein solution and make neutral by the addition, drop by drop, of a 10 per cent. solution of caustic soda. Make up to the 500 c.c. mark with distilled water and transfer to a 1,000 c.c. Erlenmeyer flask. Heat on a water bath under a reflex condensor to bring all soluble matter into solution, shaking

often during the boiling. Cool, add 1 c.c. of chloroform and place in the icebox over night in order to solidify the soaps of the higher fatty acids. Filter through cotton, and then filter through plaited filter, covering the funnel to prevent evaporation, as this filtration may require several hours. Add 20 drops of 85 per cent. phosphoric acid and allow to stand an hour or more in the icebox. Filter through plaited filter, covering the funnel to prevent evaporation.²

Transfer 150 c.c. of the final solution, as obtained according to the above directions, to a 500 c.c. round bottom, short, ring neck, pyrex flask; attach to a steam distilling apparatus and mark the level of the liquid in the flask with a black pencil. Bring the steam generator to boiling and the contents of the 500 c.c. flask just to boiling; then allow steam to pass into the flask; light the small burner under the flask, keeping the contents of the flask at constant volume and collect the distillate in 100 c.c. flasks; titrate each 100 c.c., using tenth normal alkali and phenolphthalein. Continue the distillation until the titration value for 100 c.c. of distillate falls to less than 0.2 c.c. tenth normal alkali. Calculate final result by adding all the titration figures and multiplying this by 25/6.

For each run, save and combine all distillates after they have been titrated; concentrate to a volume of about 25 c.c. and use for the identification of the volatile acid or acids present, using the method given by Dyer,¹ or that of Mulliken.³

2. CHEMICAL EXAMINATION OF STOOLS

The amounts of water soluble and volatile acid found in the stools examined are shown in Table 2. These figures show that bottle fed infants may eliminate stools which contain much larger amounts of water soluble and volatile acid than is found in the stools from normal breast-fed infants.

Our examination of the stools from breast-fed infants has shown all stools from normal healthy breast-fed infants to have an acid reaction and that the volatile acid present is principally a mixture of acetic and formic acids. Our examination of the stools from bottle-fed infants receiving simple cow's milk modifications has shown that these stools may be acid, neutral or alkaline in reaction, and that the acid stools from such infants contain a volatile acid which we have identified as acetic acid.

2. In order to expedite filtration we modified our procedure by adding 10 gm. animal charcoal, shaking well, and centrifuging before filtering. In this manner we were able to filter the solution quite rapidly, but were troubled by bumping during distillation due to the precipitation of insoluble calcium phosphate in the flask. For this reason we reverted to the original method, arranging our work so as to allow plenty of time for the filtration.

3. Mulliken: Identification of Pure Organic Compounds, New York, John Wiley & Sons, Ed. 1, 1904, p. 80.

TABLE 2.—ACID STOOLS FROM INFANTS. WATER SOLUBLE ACIDITY AND VOLATILE ACID CONTENT OF STOOLS FROM TWENTY-FOUR HOURS' AMOUNT OF FOOD

Breast-Fed				Bottle-Fed, Cow's Milk, Acid Stools Only			
Number	Water Soluble Acidity, C.c. N/10	Volatile Acid Content, C.c. N/10	Predominating Volatile Acids	Number	Water Soluble Acidity C.c. N/10	Volatile Acid Content, C.c. N/10	Predominating Volatile Acids
33	29.0	11.9	Formic and acetic	1	147.5	Acetic
35	23.0	17.9	Formic and acetic	3	69.0	Acetic
36	22.0	37.0	Formic and acetic	5	46.2	Acetic
43	26.0	95.5	Formic and acetic	6	48.5	Acetic
46	27.5	34.6	Formic and acetic	9	90.0	Acetic
48	52.3	58.1	Formic and acetic	3390	23.0	69.0	Acetic
50	26.9	76.4	Formic and acetic	3507	121.0	151.3	Acetic
62	55.7	66.5	Formic and acetic	3416	35.1	46.2	Acetic
63	22.8	57.8	Formic and acetic	3464	108.9	121.4	Acetic
65	12.1	37.1	Formic and acetic	3484	244.0	147.5	Acetic
66	17.8	79.9	Formic and acetic	3316	16.9	48.5	Acetic
67	23.5	56.8	Formic and acetic	3358	75.6	85.0	Acetic
68	43.6	49.8	Formic and acetic	3337	59.0	60.1	Acetic
69	16.4	31.4	Formic and acetic	3374	10.5	34.7	Acetic
70	40.0	59.5	Formic and acetic	3357	6.0	27.4	Acetic
71	25.0	42.6	Formic and acetic	3495	7.0	19.8	Acetic
72	21.9	42.5	Formic and acetic	3317	6.0	31.5	Acetic
74	20.0	53.8	Formic and acetic	3395	49.0	39.3	Acetic
75	22.5	33.5	Formic and acetic	3407	138.0	149.7	Acetic

TABLE 3.—TITRATION VALUES FOR DISTILLATION OF FATTY ACIDS OF FECES FROM BREAST-FED BABIES AND BABIES RECEIVING MODIFIED MILK FORMULAE

Volume Distilled	Breast-Fed Baby 67			Baby Fed on Modified Milk Formulae		
	Titration for Each 100 C.c. Portion	Total Titration	Percentage of Total	Titration for Each 100 C.c. Portion	Total Titration	Percentage of Total
100	3.27	3.27	23.93	11.08	11.08	38.70
200	2.55	5.82	42.60	6.15	17.23	60.18
300	1.90	7.72	56.51	3.72	20.95	73.17
400	1.50	9.22	67.50	2.35	23.30	81.38
500	1.11	10.33	75.63	1.61	24.91	86.98
600	0.85	11.18	81.84	1.11	26.02	90.88
700	0.62	11.80	86.37	0.74	26.76	93.47
800	0.47	12.27	89.82	0.55	27.31	95.37
900	0.36	12.63	92.45	0.39	27.70	96.74
1000	0.28	12.91	94.50	0.33	28.03	97.89
1100	0.24	13.15	96.27	0.24	28.27	98.73
1200	0.19	13.34	97.66	0.23	28.50	99.55
1300	0.19	13.53	99.05	0.13	28.63	100.00
1400	0.13	13.66	100.00			

In our graphic study of the rate of distillation of the volatile acids in the stools we obtained results which are shown by the two typical cases listed in Table 3.

In the case of the breast-fed babies the curves were all found to lie between the curves for pure formic and pure acetic acids. In order to avoid the confusion produced by the plotting of all the curves on one sheet we have made a composite curve which is given as Figure 2. This is nearly a straight line, lying between the formic and acetic acid lines.

In the case of the acid stools from bottle-fed babies the curves were found to lie to the left of the acetic acid curve, indicating a slight amount of higher volatile acid. This is shown in Figure 3.

The marked difference in the nature of the volatile acid present in the two types of stools examined by us has led us to seek for the cause. Our first thoughts turned toward the intestinal bacteriology of the two types of infants under discussion.

BACTERIOLOGY OF INFANTS' STOOLS

The splendid pioneer work of Escherich on the bacteriology of nurslings' stools revealed the fact that the typical flora of these stools was quite different from the flora of the stools of artificially fed infants.

Kendall⁴ has summarized this work and that of other investigators very well. He states that culturally, morphologically, and chemically the intestinal flora of breast-fed infants is more homogeneous than that of artificially fed infants.

In addition to *Bacillus bifidus* and *Bacillus acidophilus*, which comprise a majority of the characteristic intestinal bacteria, small numbers of *Micrococcus ovalis*, *Bacillus coli*, *Bacillus lactis aerogenes* and other bacteria are found in the feces of nurslings.

The most distinctive features of the dejecta of artificially fed infants are: the relative increase of gram-negative bacteria of the coli-aerogenes type and of coccal forms of the *Micrococcus ovalis* type, together with a diminution of *Bacillus bifidus*. *B. acidophilus* is relatively more numerous, as a rule, in the artificially fed infant than in the nursling. Proteolytic bacteria of several types are also of frequent occurrence, but they are not commonly found in the dejecta of normal nurslings.

We have made similar observations, finding a predominatingly gram-positive flora in breast milk stools as contrasted with a distinctly gram-negative flora in the dejecta of artificially fed infants.

In the case of nurslings *B. bifidus* is so prominent that from the examination of a direct smear one might consider it to be present in almost pure culture. Closer investigation together with cultural work shows the presence of small numbers of the coli-aerogenes type, *Micrococcus ovalis* and spore bearers.

On the other hand, both direct smears and cultures show that the prominent organisms of the stools of artificially fed infants are those of the coli-aerogenes type (including *B. coli*, *B. aerogenes*, *B. acidi*

4. Kendall: Bacteriology, Philadelphia, Lea and Febiger, pp. 584-585.

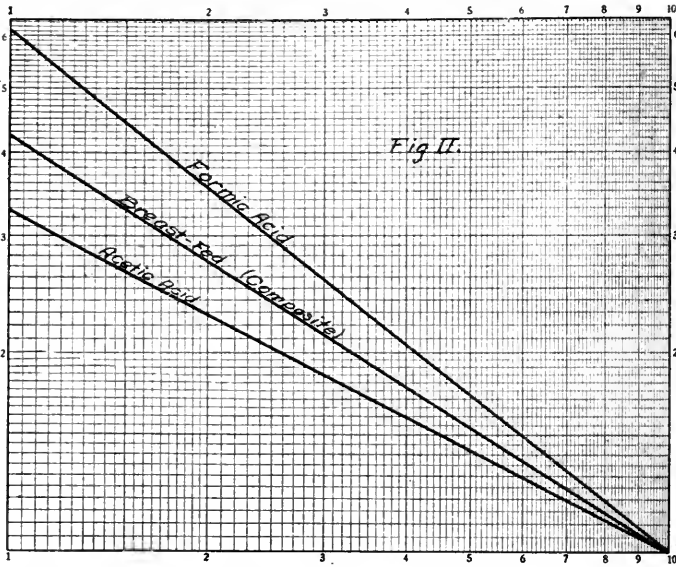


Fig. 2.—Composite distillation curve for breast-fed stools compared with curves for acetic and formic acids.

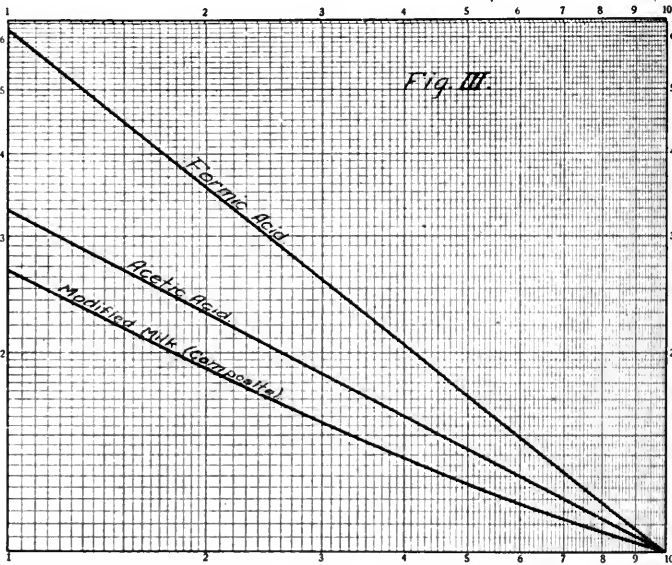


Fig. 3.—Composite distillation curve for modified milk stools compared with curves for acetic and formic acids.

lactici, *B. cloacae* and *B. capsulatus*) and *Micrococcus ovalis*. Smaller numbers of subtiloid organisms, *B. pyocyaneus* and *B. alkaligenes* were isolated.

Bosworth and Prucha⁵ have shown that *B. aerogenes*, one of the most common of the dairy organisms, has the peculiar property of decomposing citric acid, the final end products being water, carbon dioxid and acetic acid. We have found that pure cultures of *B. aerogenes* isolated from the stools of several infants possessed the power of decomposing citric acid in the exact quantitative manner previously shown by Bosworth and Prucha who used cultures of this organism isolated from dairy products.

Our finding that *B. aerogenes* is one of the most common organisms present in the feces from bottle-fed babies, together with the fact that cow's milk, as shown by Bosworth and Van Slyke, contains 0.2 per cent. citric acid, led us to investigate the possible connection which might exist between the presence of citric acid in modified cow's milk and the presence of acetic acid and *B. aerogenes* in the type of stool under discussion.

The question also arose as to whether other fecal organisms might not have this same power of decomposing citric acid with acetic acid as one of the end products. To ascertain this point experiments were undertaken.

Volatile Acids Resulting from the Action of Certain Aerobic Bacteria on Citric Acid.—Fresh specimens were obtained frequently from the babies in the hospital and as many different types of bacteria were isolated and identified as possible.

One hundred c.c. of plain beef extract broth containing 1 per cent. crystallized sodium citrate, with controls of this same broth without the citrate, were inoculated with pure cultures of the different organisms and allowed to grow for several days at 37 C. On distillation with steam after acidifying with sulphuric acid, volatile acid was recovered.

From Table 4 it will be seen that some organisms produced more volatile acid than others, for instance: *B. aerogenes* (No. 6.6), *M. ovalis* (No. 58.4), and an unidentified organism (No. 23.3) produced more than 0.4 gm. of the volatile acid calculated as acetic acid; while *B. capsulatus* (No. 33.4), *B. cloacae* (No. 21.1), *B. coli*, and *B. acidilactici* (No. 39.4) produced smaller amounts, from 0.15 to 0.22 gm.; and a third class of nonsugar fermenters like *B. subtilis* and *B. alkaligenes* produce practically none, which indicates that the power of producing acetic acid from citric acid is peculiar to only a few organisms.

It will also be noticed that in the controls containing no citrate an appreciable amount of volatile acid was produced, possibly due to the

5. Bosworth and Prucha: J. Biol. Chem. 8:479, 1910.

breaking down of the peptone contained in the medium. It is apparent that those organisms which produced large amounts of volatile acid from the citrate solution also produced relatively large amounts from the controls, showing that in the absence of citrate in the medium other constituents were attacked.

TABLE 4.—SHOWING DECOMPOSITION OF CITRATE TO ACETIC ACID (?) IN PLAIN BROTH CONTAINING SODIUM CITRATE

Name	Lab. No.	Volatile Acid			Control: No Citric Acid in Media Volatile Acid		
		Days	C.c. N/10 NaOH	Gm. as Acetic Acid	Days	C.c. N/10 NaOH	Gm. as Acetic Acid
B. aerogenes.....	6.6	4	77	0.462	14	15.4	0.092
		8	78	0.468			
		18	28.6	0.168			
B. aerogenes.....	51.1	5	65.1	0.390	10	0.0	0.000
		8	60	0.36			
B. aerogenes.....	53.3	8	20	0.12	17	4.0	0.0024
		11	24.3	0.143			
		14	66.0	0.396			
B. coli.....	7	11	41.0	0.249			
B. coli.....	8	4	18.5	0.111			
		9	44	0.264			
		15	10	0.06			
B. acidophilus.....	2	5	0.0	0.0			
		7	5.0	0.03			
		19	25.2	0.15			
B. alkaligenes.....	15.4	6	0.6	0.0036	8	0.8	0.0048
		8	1.0	0.006			
B. cloacae.....	21.1	4	37.8	0.226	14	0.5	0.008
		8	44	0.264			
M. ovalis.....	58.4	6	91.8	0.546	15	13.1	0.078
		14	87.5	0.52			
B. capsulatus.....	33.4	5	25	0.15	15	13.1	0.18
		14	31.8	0.18			
B. acid lactici.....	39.4	5	25	0.15			
		14	9.3	0.055			
Subtiloid organism.....	45.5	5	0.0	11	1.5	0.009
		11	2.2	0.013			
B. morgani I.....	24.4	5	30.0	0.18	12	2.8	0.0168
		8	27.2	0.143			
Coccus.....	59.4	6	4.0	0.024	12	2.1	0.012
		8	1.4	0.084			
		12	5.6	0.033			
Unidentified.....	23.3	5	72.5	0.435	16	6.0	0.036
		11	66.5	0.399			
		14	74.6	0.447			
Unidentified.....	34.4	5	5.0	0.03	16	0.5	0.008
		12	17.9	0.105			
Unidentified.....	36.3	6	37.1	0.222	8	2.2	0.013
		8	22.2	0.133			

In an effort to obtain quantitative data the medium used by Bosworth and Prucha⁵ was tried. This medium was made according to the following formula:

MEDIUM 1: Acid sodium phosphate, 5 gm.; magnesium sulphate, 5 gm.; potassium chlorid, 0.5 gm.; official ammonium citrate solution⁵ 50 c.c.; water to make 1,000 c.c.

B. aerogenes and Organism 23.3 grew luxuriantly in this medium within twenty-four hours, but other organisms grew only faintly or not at all.

Portions of this medium were inoculated with pure cultures of those organisms which thrived in it and after three or four days were

tested for citric acid. As soon as all the citrate had disappeared, 100 c.c. were distilled with steam after acidifying with sulphuric acid and the volatile acid recovered and identified by the formation of acet-p-toluide.

The results are tabulated in Table 5 and they show that while all the organisms tested destroyed the citric acid, only two of them, *B. aerogenes* and the unidentified Organism 23.3, produced acetic acid.

TABLE 5.—SHOWING DECOMPOSITION OF CITRIC TO ACETIC ACID IN MEDIUM 1

Name	Lab. No.	Time Citric Acid Disappeared, Days	Volatile Acid		Melting Point of Toluide
			C.c. N/10 NaOH	Gm. as Acetic Acid	
<i>B. aerogenes</i>	4	5	88.5	0.531	147
<i>B. aerogenes</i>	6.6	4	80.0	0.48	147
<i>B. aerogenes</i>	42.3	8	79.0	0.479	147
<i>B. aerogenes</i>	20.6	3	87.0	0.52	147
<i>B. aerogenes</i>	13.1	7	70.0	0.42	146
<i>B. aerogenes</i>	38.4	5	70.0	0.42	146
<i>B. aerogenes</i>	20.7	4	11.5	0.429	147
Unidentified.....	23.3	4	70.0	0.42	147
<i>Coccus</i>	44.3	12	0.0	0.00	
Unidentified.....	58.3	13	0.4	0.0024	
Unidentified.....	34.4	11	0.5	0.003	

As the Bosworth and Prucha medium proved unsatisfactory for the growth of all but a few organisms, it was modified by the addition of 0.3 per cent. beef extract.

MEDIUM 2: Acid sodium phosphate, 5 gm.; magnesium sulphate, 5 gm.; potassium chlorid, 0.5 gm.; official ammonium citrate solution⁵ 50 c.c.; Liebig's beef extract, 3 gm.; water to make 1,000 c.c.

This medium was inoculated with pure cultures and good growths were obtained. The growths were tested for volatile acid and the results are given in Table 6.

Only one organism (No. 58.4), which is probably *M. ovalis*, produced acetic acid. The others, including *B. cloacae*, *B. coli*, *B. capsulatus*, *B. acidilactici* and several unidentified organisms, required more or less time, ranging from three to fourteen days, to dispose of the citrate but produced no acetic acid.

Study of the Source of Formic Acid.—In order to determine the source of formic acid which we found to be present in the stools from breast-fed babies we referred to the study of the bacterial flora of the feces of breast-fed babies which has been conducted by Brown and Bosworth.⁶ As such feces show a characteristic predominance of *B. bifidus*, we conducted an investigation of the metabolism of *B. bifidus* in the presence of citric acid in order to determine if this organism in the process of decomposing citric acid produces formic acid.

After several unsuccessful attempts, growth was produced in a neutral beef extract broth medium containing 1/2 per cent. sodium

6. Brown, E. W., and Bosworth, A. W.: Am. J. Dis. Child. **23**:243 (March) 1922.

citrate. One specimen produced sufficient volatile acid to give a good curve (Fig. 4).

The curve of the fatty acids from *B. bifidus* is neither a formic acid curve nor an acetic acid curve nor does it coincide with the composite curve for fatty acids from the stools of breast-fed babies. It lies to the left of the composite, therefore indicating a greater percentage of acetic acid than does the average stool from breast-fed babies. It appears that there may be present in the intestines some other organism which can produce a higher percentage of formic acid than does *B. bifidus*, or else the percentage of formic acid produced varies with changing conditions in the intestinal tract. It is to be regretted that circumstances prevent the authors from definitely

TABLE 6.—SHOWING DECOMPOSITION OF CITRIC TO ACETIC ACID IN MEDIUM 2

Name	Culture No.	Time Citric Acid Disappeared, Days	Volatile Acid		Melting Point of Toluide
			C.c. N/10 NaOH	Gm. as Acetic Acid	
<i>M. ovalis</i>	58.4	10	59.0	0.354	147
<i>B. coll.</i>	7	10	0.4	0.0024	
<i>B. coli</i>	26.1	14	1.2	0.0072	
<i>B. coli</i>	60.1	4	0.35	0.0021	
<i>B. coli</i>	58.2	8	20.0	0.12	
<i>B. morgans I.</i>	24.4	18	0.7	0.0042	
<i>B. morgans I.</i>	39.7	21	0.4	0.0024	
<i>B. morgans I.</i>	21.5	14	4.7	0.0282	
<i>B. cloacae</i>	21.1	4	1.0	0.006	
<i>B. cloacae</i>	20.1	3	0.1	0.0006	
<i>B. capsulatus</i>	33.4	4	0.4	0.0024	
<i>B. capsulatus</i>	17.6	3	0.5	0.0003	
<i>B. acidilactici</i>	4.3	4	0.7	0.0042	
<i>B. acidilactici</i>	14.1	18	0.5	0.0030	
Dysentery-like.....	34.1	4	0.2	0.0012	
<i>B. acidophilus</i>	2	4	0.7	0.0042	
<i>Coccus</i>	44.3	3	0.3	0.0018	
<i>B. proteus</i>	stock cult. 27				
<i>B. proteus vulgaris</i>	28				
Unidentified.....	34.4	4	0.3	0.0018	
Unidentified.....	36.3	4	0.35	0.0021	
Unidentified.....	23.1	3	0.6	0.0036	
Unidentified.....	23.4	3	0.2	0.0012	

answering, for the present, this most interesting and important question. It must suffice for the present to offer the suggestion that our observations indicate that *B. bifidus* may attack citric acid with the production of two acetic acid molecules and one formic acid molecule for each molecule of citric acid.

Can the Acetic Acid Content of Infants' Stools Be Increased by the Addition of Citrate to the Food?—Our finding that certain organisms, present in the stools from bottle-fed infants, possess the property of producing acetic acid from citric acid has led us to investigate the possibility of increasing the acetic acid content of stools by the addition of citrate to the food. This was done in the manner indicated in Table 7.

In connection with the data given in Table 5 it is of interest to note the following facts: When a synthetic food containing no citrate is fed to an infant, no acetic acid appears in the stools; when the same food containing a soluble citrate (sodium citrate) is fed, a small amount of acetic acid appears in the stools; and when the same food containing an insoluble citrate (calcium citrate) is fed a large amount of acetic acid appears in the stools.

The addition of soluble citrates (sodium citrate or orange juice) to modified milk formulas increases only slightly the acetic acid contents of the stools, while the addition of an insoluble citrate (calcium citrate) to the same formulas results in a marked increase in the acetic acid contents of the stools.

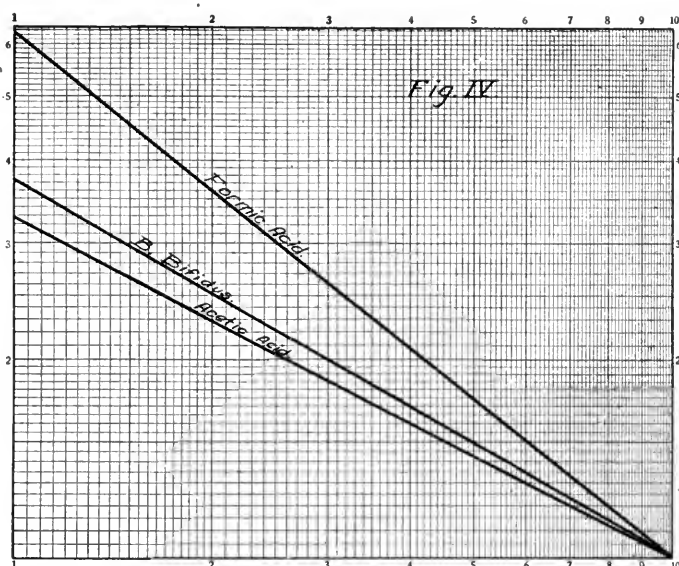


Fig. 4.—Distillation curve from culture of *B. bifidus* compared with curves for acetic and formic acids.

The stools from infants receiving Dryco dry milk contain large amounts of acetic acid. This is probably due to the fact that a considerable portion of the soluble citrate, originally present in the milk, is converted to insoluble calcium citrate during the process of drying.

The explanation offered for the observations contained in this paper are as follows: While cow's milk, like human milk, contains about 0.2 per cent. citric acid, present in the form of soluble citrates, cow's milk, unlike human milk, contains a considerable quantity of soluble calcium salts in its whey or serum. Milk, on entering the intestines, encounters an alkaline or neutral condition and this condition induces a chemical rearrangement among the milk constituents which results, in

the case of cow's milk, in the precipitation of insoluble calcium citrate. As this insoluble calcium citrate cannot be absorbed by the intestines, it becomes part of the waste matter which moves along the whole intestinal tract. Here it is subjected to attack by the bacteria present with the results noted in this paper.

There may be some clinical significance to the presence of the insoluble citrate in the intestines if we remember that citrates, as shown by Bosworth and Prucha, may take the place of sugar for certain organisms and, therefore, acting as a protein sparer, prevent or retard putrification within the intestines, an important point to be considered in view of the recent work of one of us,⁷ which shows

TABLE 7.—SHOWING RELATION OF ACETIC ACID IN STOOLS TO CITRATE IN FOOD

Case No.	Kind of Food	Formula F-S-P	Volume of Food per 24 Hrs., C.c.	Amount of Citric Acid in Milk per 24 Hrs., Gm.	Amount and Kind of Citrate Added per 24 Hours	Acetic Acid in Stools, Gm. per 24 Hours	Reaction of Stools Toward Litmus Paper
475	"Synthetic milk"	2-5-1.6	1,440	None	None	None*	Alkaline and neutral
475	"Synthetic milk"	3-6-1.6	1,440	None	2.88 gm. of sodium citrate	0.370	Acid and neutral
475	"Synthetic milk"	3-6-1.6	1,440	None	1.5 gm. of calcium citrate	0.642	Acid
475	Modified milk	2-6-1.6	1,440	1.44	None	0.855	Acid
475	Modified milk	2-6-1.6	1,440	1.44	1.5 gm. of calcium citrate	1.213	Strongly acid
479	Modified milk	2-5-1.6	1,440	1.44	None	0.278	Acid
479	Modified milk	2-5-1.6	1,440	1.44	2 gm. of sodium citrate	0.372	Acid
479	Modified milk	2-5-1.6	1,440	1.44	2 gm. of calcium citrate	0.840	Strongly acid
489	Modified milk	2.5-6.5-2	1,080	1.24	None	0.540	Acid
489	Modified milk	2.5-6.5-2	1,080	1.34	Orange juice	0.640	Acid
493	Dryco dry milk	1.2-4.4-3.4	1,000	2.13	None	0.907	Alkaline

* Contained a small amount of volatile acid which was not acetic acid.

that the feces from bottle-fed infants contain more nitrogenous matter than is the case with breast-fed infants.

Another point to be considered also is what detrimental effect the loss of the citrate may produce. Citric acid is a normal constituent of both human milk and cow's milk. Its presence in milk may be taken as an indication that it serves some purpose in the animal metabolism. Citric acid is not only an acid but it is also an alcohol as may be seen from its structure.

As an alcohol it may form esters and in this connection the destructive action of heat upon the antiscorbutic vitamin in milk would suggest the possibility that this vitamin may be an ester-like compound of some of the citric acid in milk.

7. Bosworth, A. W.: Am. J. Dis. Child. **22**:613 (Dec.) 1921.

SUMMARY

1. A method is given for the distillation of volatile acids from infants' stools.

2. A graphic method is given for the study of the nature of the volatile acids which may be distilled from infants' stools.

3. The stools from normal healthy breast-fed infants have been found to be acid in reaction and to contain the volatile acids, formic and acetic.

4. The stools from healthy bottle-fed infants have been found to be acid, neutral or alkaline in reaction. The acid stools may contain very large amounts of acid and the volatile acid present is acetic acid.

5. *B. aerogenes*, *M. ovalis*, *B. bifidus*, and other unidentified organisms isolated from acid stools of babies possess the power of reducing citrate to a volatile acid.

6. The volatile acid produced by *B. aerogenes*, *M. ovalis*, and other unidentified organisms was determined to be acetic acid.

7. The volatile acid produced by *B. bifidus* was determined to be a mixture of acetic and formic acids.

8. Other organisms like *B. coli*, *B. capsulatus*, *B. acidi lactici*, and *B. cloacae* disposed of the citrate producing carbon-dioxid and water without the formation of acetic acid.

9. If a synthetic food containing no citrate is fed to an infant, no acetic acid appears in the stools.

10. If a synthetic food containing a soluble citrate (sodium citrate) is fed to an infant, a small amount of acetic acid appears in the stools.

11. If a synthetic food containing an insoluble citrate (calcium citrate) is fed to an infant a large amount of acetic acid appears in the stools.

12. The addition of soluble citrates (sodium citrate or orange juice) to modified milk formula increases only slightly the acetic acid contents of the stools.

13. The addition of an insoluble citrate (calcium citrate) to modified milk formulas results in a marked increase in the acetic acid content of the stools.

14. The stools from infants receiving Dryco dry milk contain large amounts of acetic acid. This is probably due to the fact that a considerable portion of the soluble citrate, originally present in the milk, is converted to insoluble calcium citrate during the process of drying.

PROGRESS IN PEDIATRICS

REVIEW OF THE LITERATURE ON RESPIRATORY DISEASES FROM JANUARY, 1920, TO JUNE, 1921 *

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NEW YORK CITY

(Concluded from page 282)

PNEUMONIA

Pathogenesis.—The studies on experimental pneumonia of Cecil and Blake⁶³ comprise an unusually important series of articles. These articles deserve a very careful reading as does also a single article by Cecil⁶⁴ which gives a short and excellent exposition of the bacteriology and mode of infection of pneumonia. These investigators concluded that while the pneumococcus is the specific cause of lobar pneumonia, it is unable to initiate an infection of the normal mucous membranes of the upper respiratory tract, or to produce pneumonia following intravenous injection, but it must gain access to the lower respiratory tract by way of the trachea in order to cause pneumonia. Lobar pneumonia is therefore bronchiogenic in origin, the invasion of the bloodstream by pneumococci in this disease being secondary to the invasion of the lungs. The pneumococcus primarily invades the lung tissue at some point or points near the root of the lobe, and thence spreads throughout the lobe by way of the perivascular, peribronchial and septal tissues, and the lymphatic system. The alveolar structure

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* From the Department of Pediatrics of Cornell University Medical College.

* This review was originally undertaken by Dr. Louis C. Schroeder, but after reviewing more than fifty articles, he was forced by pressure of other work to relinquish this study. He very generously contributed his notes to me for which I make grateful acknowledgment.

63. Cecil, R. L., and Blake, F. G.: Studies on Experimental Pneumonia: I. Production of Pneumococcus Lobar Pneumonia in Monkeys, *J. Exper. M.* **31**: 403 (April) 1920. II. Pathology and Pathogenesis of Pneumococcus Lobar Pneumonia in Monkeys, *Id.* **31**:445 (April) 1920. III. Spontaneous Pneumonia in Monkeys, *Id.* **31**:499 (May) 1920. IV. Results of Prophylactic Vaccination against Pneumococcus Pneumonia in Monkeys, *Id.* **31**:519 (May) 1920. V. Active Immunity against Experimental Pneumococcus Pneumonia in Monkeys Following Vaccination with Living Cultures of Pneumococcus, *Id.* **31**:657 (June) 1920. VI. Active Immunity Following Experimental Pneumococcus Pneumonia in Monkeys, *Id.* **31**:685 (June) 1920. VII. Treatment of Experimental Pneumococcus Type I Pneumonia in Monkeys with Antipneumococcic Serum, *Id.* **32**:1 (July) 1920. VIII. Experimental Streptococcus Hemolyticus Pneumonia in Monkeys, *Id.* **32**:401 (Oct.) 1920.

64. Cecil, R. L.: Bacteriology and Pathogenesis of Pneumonia, *New York M. J.* **113**:728 (May 18) 1921.

becomes primarily infected by spread of the pneumococci from the grosser framework of the lungs into the alveolar walls, and thence into the alveolar spaces with the exudate. Hepatization usually occurs first in the posterior and upper parts of the lower lobes, in the lower part of the middle lobe, and in the lower and posterior parts of the upper lobe.

Cecil and Blake further stated that the mode of infection in *Streptococcus hemolyticus* pneumonias is similar to that in the pneumococcus pneumonias, as above, but while the influenza bacillus enters by passing down the bronchial tree, it lacks the invasive character of the other two microorganisms. Hence, the lesions produced by this bacillus are focal while those produced by the pneumococcus and the streptococcus involve extensive areas.

Cecil urged discarding the terms "bronchopneumonia" and "lobar pneumonia" for *Streptococcus hemolyticus* or *S. viridans* pneumonia, pneumococcus pneumonia, influenza bacillus pneumonia, etc.

Wherry and Butterfield⁶⁵ were not able to produce pneumonia in mice after spraying with virulent pneumococci. Their experiments showed that the type M 5 of the *Bacillus enteritidis* is inhaled by mice into the deepest alveoli or capillary bronchi of the lungs, and that primary pneumonia follows in the case of this microorganism, which is capable of growing and producing its toxins there, whereas the virulent pneumococci gradually disappear.

Foster⁶⁶ stated that any circumstance which lowers the vitality of the human organism as a whole, or by irritation injures the pulmonary tissues locally, predisposes to a primary bronchopneumonia. The invader is always at hand and the invasion depends on the host. He called attention to the fact that primary bronchopneumonia is not limited to childhood and old age but is a common affection in young robust adults, though easily overlooked.

Bacteriology of Pneumococcus Pneumonias.—Spooner⁶⁷ tabulated the statistics found by eleven authors as to the relative frequency of occurrence of the various types of the pneumococci in lobar pneumonia. Of a total of 2,980 cases, 29 per cent. were Type I; 21 per cent. were Type II; 11 per cent. were Type III, and 39 per cent. were Type IV. He urged the careful use of Type I serum in the treatment of Type I cases.

65. Wherry, W. B., and Butterfield, C. T.: Inhalation Experiments on Influenza and Pneumonia, and on the Importance of Sprayborne Bacteria in Respiratory Infections, *J. Infect. Dis.* **27**:315 (Oct.) 1920.

66. Foster, N. B.: Notes on the Diagnosis of Bronchopneumonia and Its Complications, *Am. J. M. Sc.* **161**:1 (Jan.) 1921.

67. Spooner, L. H.: The Specific Diagnosis and Treatment of Acute Lobar Pneumonia, *Boston M. & S. J.* **182**:389 (April 15) 1920.

Locke, Thomas, and O'Hara⁶⁸ reported that they had on their pneumonia service at the Boston City Hospital, ninety-four cases of lobar pneumonia in children under 15 years of age of which only four died. Forty-two cases were typed, and revealed that of these, eleven were Type I; five were Type II; four were Type III, and twenty-two were Type IV. Of the four fatal cases, two were untyped, one was Type I and one was Type IV. Because of the low mortality, no antipneumococcus treatment was given to those patients who were under 5 years of age.

Armstrong⁶⁹ in England reported rather contradictory findings to those of the Boston investigators. He noted that the Type I pneumococcus, though responsible for many cases of lobar pneumonia in adults, does not appear to cause the disease in childhood. In only one case was a Type I pneumococcus isolated from a child. The pneumococci he found most responsible for the disease in young children belonged almost uniformly to Type II. Type III seemed in the upper respiratory tract to have only a limited distribution.

For rapid pneumococcus typing, Oliver⁷⁰ described a precipitin test of filtered pneumonic sputum to which bile has been added. By this method the typing may be effected within half an hour after the receipt of the sputum.

According to Nobécourt, Paraf and Bonnet,⁷¹ at the Paris Maternité, during 1919, all the infants and adults were systematically examined for pneumococci with 55 per cent. positive results from 322 smears. Type III was found in 133 cases and was responsible for most of the infections. When a carrier of Type II had been admitted to the ward, this type appeared almost at once in the other women and infants and a train of infectious processes in the upper air passages followed. They considered it especially important to guard infants against this infection. The infant should be taken away from its mother if the latter becomes affected and be brought to her only to be nursed, and the mother should wear a veil while nursing.

Sailer, Hall, Wilson and McCoy,⁷² reported a study of pneumococcus carriers. They believe strongly that active methods of disinfection should be carried out against pneumococcus carriers and that

68. Locke, E. A.; Thomas, H. M. Jr., and O'Hara, D.: *Acute Respiratory Infections at the Boston City Hospital*, Boston M. & S. J. **183**:480 (Oct. 21) 1920.

69. Armstrong, R. R.: *The Serologic Characters of Disease-Producing Pneumococci*, Brit. M. J. **1**:259 (Feb. 19) 1921.

70. Oliver, W. W.: *A Rapid Method of Pneumococcus Typing*, J. Infect. Dis. **27**:310 (Oct.) 1920.

71. Nobécourt, P.; Paraf, J., and Bonnet, H.: *Pneumococcus Infection in Infants*, Presse Méd. **28**:313 (May) 1920. Abstr. J. A. M. A. **75**:137, July 10) 1920.

72. Sailer, J.; Hall, M. W.; Wilson, R. L., and McCoy, C.: *A Study of Pneumococcus Carriers*, Arch. Int. Med. **24**:600 (Dec. 15) 1919.

all contacts of cases of pneumonia should be cultured as are meningitis contacts. They described the results of numerous means of disinfection, the most valuable of which proving to be oily solutions of phenol and iodine.

Thomas and Parker⁷³ studied the bacteriology of lobar pneumonia by means of lung punctures. They found, according to Locke, Thomas and O'Hara,⁶⁸ a mortality of 56 per cent. in cases in which viable organisms were obtained by lung puncture after the fifth day of the disease, whereas cases which yielded no organisms by lung puncture irrespective of the day of the disease, recovered with only two exceptions, or 6.5 per cent. They found that destruction of the organisms is the first step in the process of recovery, but also that crisis may occur before the organisms have been entirely killed, or not until several days after. This led them to the belief that the antibacterial forces may proceed at one rate of speed while the detoxifying mechanism is going on at a different rate, and they concluded that the death of the pneumococcus is not the factor which causes or initiates crisis.

Pathology.—Berry⁷⁴ made a careful analysis of the necropsy findings in 400 fatal cases of lobar pneumonia, and noted a number of outstanding features, of which several are already well recognized. He noted, however, that the pericardium is affected in varying degree in almost one third of the cases, but that true acute nephritis as a complication or sequel of lobar pneumonia is unusual, if not rare. He found that the products formed or eliminated by, or as a result of the pneumococcus and occasional other organisms in lobar pneumonia, produce a general toxemia with definite reactions and lesions in many organs of the body. Grossly, these changes are best and most frequently seen in the spleen, kidneys, liver and heart, whereas histologically they are found still more commonly in the suprarenals and pancreas. Acute sinusitis and otitis media are decidedly uncommon in lobar pneumonia in adults, which fact he feels would strengthen the idea suggested by Blake and Cecil, that the pneumococcus by itself is of relatively low pathogenicity for the upper respiratory tract.

Meakins⁷⁵ studied a number of cases of pneumonia to determine the quantity and quality of the expired air and found that as the respiration increased, there was a gradual decrease in the volume per respiration though the total ventilation per minute showed a conspicuous increase.

73. Thomas, H. M., Jr., and Parker, F. Jr.: Results of Antimortem Lung Punctures in Lobar Pneumonia: Their Bearing on the Mechanism of Crisis, *Arch. Int. Med.* **26**:125 (July) 1920.

74. Berry, F. B.: Lobar Pneumonia: An Analysis of 400 Autopsies, *M. Clinics N. America* **4**:571 (Sept.) 1920.

75. Meakins, J.: Harmful Effects of Shallow Breathing with Special Reference to Pneumonia, *Arch. Int. Med.* **25**:1 (Jan.) 1920.

He concluded that the point might be reached where the alveolar air inspired or expired might amount to a comparatively few cubic centimeters, being undoubtedly insufficient to carry on adequate pulmonary ventilation so that eventually anoxemia and cyanosis would develop. He further noticed in his cases that with increased respiration, the oxygen content of the expired air became higher and the carbon dioxide content lower so that a respiratory quotient above one occurred. But with crisis there was a rapid return to normal not only of respiratory quotient but also of respiratory rate, respiratory volume and total ventilation per minute. He thought it not probable that this is due to any conspicuous change in the damaged lung. He concluded, therefore, that the anoxemia and cyanosis occurring in lobar pneumonia is the result of the rapid and shallow breathing typical of the condition, and he also noted the well recognized harmful effect of persistent anoxemia on the cardiovascular system.

Methemoglobin in pneumonia was studied by Stadie⁷⁶ who noted that in the occasional cases of this disease which show a decrease in the oxygen capacity of the blood, the decrease is probably due to a formation of methemoglobin. The latter is removed from the circulation, however, as rapidly as it is formed, so that it can seldom be detected even qualitatively, and is probably never a cause of cyanosis.

A study of water retention in pneumonia was made by Lussky and Friedstein⁷⁷ who called attention to the fact that coincident with defervescence in febrile diseases there is a loss of weight, and that this loss is especially likely to occur in pneumonia. They were unable to find any relationship between the rapidity of the loss and either the degree or the duration of the fever. The absorption and excretion of the inflammatory exudate or of its products, as shown by an increased amount of urine as well as by the excreted amounts of chlorids and nitrogen, cannot explain the whole story. They are of the belief that the loss of weight coincident with or slightly preceding the abrupt fall in temperature is best explained by the theory that water which is usually at the disposal of the organism for purposes of heat regulation becomes not available for this purpose, being possibly bound within the organism in such a way that it cannot exercise its heat dissipating function by evaporation from the body surfaces and lungs. With restoration of the water binding power of the tissues to the normal, which may occur more or less abruptly, water would be liberated for heat regulatory purposes and elimination in the urine.

76. Stadie, W. C.: Studies in Blood Changes in Pneumococcus Infection. An Experimental Study of the Formation and Fate of Methemoglobin in the Blood, *J. Exper. M.* **33**:627 (May) 1921.

77. Lussky, H. O., and Friedstein, H.: Water Retention in Pneumonia, *Am. J. Dis. Child.* **19**:337 (May) 1920.

In this way, the loss of weight coincident or shortly preceding the abrupt fall of temperature could be explained.

Symptomatology, Diagnosis and Occurrence.—Abrahams⁷⁸ made a clinical summary of 558 cases of untyped lobar pneumonia seen among the soldiers of the British Army command at Aldershot during 2½ years of the war period. The initial symptoms or complaints he tabulated as follows:

Shivering, 69 per cent.; pain in side, 60 per cent.; headache, 35.6 per cent.; vomiting, 33 per cent.; cough, 24 per cent.; pains all over, 9 per cent.; general malaise, 7.6 per cent.; bronchitis, 7 per cent.; pain in abdomen,⁷⁹ 5.5 per cent.; tonsillitis, 2.3 per cent.; dyspnea, 2 per cent.; hemoptysis, 1.6 per cent.; diarrhea and vomiting, 0.5 per cent.

Wilcox⁸⁰ called renewed attention in his study of the symptomatology of childhood to the fact that the physical signs of the chest are affected by certain structural differences peculiar to youth, such as the thin elastic chest wall, and the relatively larger space occupied by the bronchial tree. In particular, the intensified breath sounds, normally heard at the right apex anteriorly in the adult, are so much more marked in children as to make this a difficult area in which to interpret uncertain physical signs. Doubt as to the existence of a lesion at the right apex often may be cleared up by comparison of the physical signs here and in the axilla, as in the latter location physiologic conditions affecting the signs anteriorly do not obtain, while a pathological lesion of the apex of the lung should produce much the same symptoms in the axilla as anteriorly or posteriorly. He cited the case of an infant in whom the physical signs over the right apex anteriorly of distinctly impaired resonance and high pitched breath sounds with a slightly bronchovesicular element, together with a head cold, fever and increased respiratory rate, seemed all to justify the diagnosis of pneumonia in the right upper lobe. However, the physical signs were normal in the apex of the right axilla, and incision of a bulging right ear drum terminated all symptoms.

Freeman⁸¹ reproduced roentgenograms showing apparently peripheral pneumonic consolidation in three children in whom repeated examination failed to reveal any physical signs of pneumonia, not even

78. Abrahams, A.: Lobar Pneumonia: A Clinical Analysis of 558 Consecutive Cases, *Lancet* 2:543 (Sept. 11) 1920.

79. Of the thirty-one patients in whom the initial complaint was pain in the abdomen, seven were admitted as cases of appendicitis, six were sent to the operating room, and three were actually operated on, but normal appendices were found.

80. Wilcox, H. B.: Some peculiarities in the Symptomatology of Childhood, *Arch. Pediat.* 37:577 (Oct.) 1920.

81. Freeman, R. G.: Pneumonia in Infancy and Childhood without Physical Signs, *Arch. Pediat.* 37:11 (Jan.) 1920.

a markedly increased rate of respiration. In all three cases, approximately the same portion of the right upper lobe was involved, and Freeman thought that the signs were obscured because to hear them one would have to do so through the right scapula. He thought it remarkable that these children gave no signs of consolidation in the axilla.

Blauner⁸² considered the diagnosis of pneumonia in infancy and early childhood to be based distinctly on physical signs since its symptoms in children, especially the fever, may be very variable. He believed that central lobar pneumonia does not exist, and that when this pneumonia does exist, it can be found by delicate percussion though bronchial breathing will only be present if the wedge-shaped area of consolidation extending in from the cortex reaches the hilum or is in communication with a bronchus. Bronchopneumonia, however, may give no physical signs other than those of a bronchitis. In children the physical signs of resolution may be those of a quick liquefaction of the consolidation with rales redux, or the resolution may be slow, lasting from three to seven days, the physical signs melting into normal signs. Râles play a very unimportant rôle in children, and may be absent throughout a pneumonia.

Gunewardene⁸³ reported a case of central pneumonia in a child of 2 years in which the physical signs of consolidation did not appear until the ninth day, and crisis did not occur until the fourteenth day.

In a report of 200 necropsies on infants who were still-born or who died within the first week of life, Warwick⁴⁵ described four cases of bronchopneumonia of which one was that of a full term infant who lived only 2½ hours, and presented at necropsy a very typical bronchopneumonia. Smears from the lung showed polymorphonuclear leukocytes and gram-positive cocci in pairs and chains. Warwick felt that there was but little doubt that this condition developed in utero although the mother appeared to be entirely normal.

Nobécourt⁸⁴ discussed the cases of two children of 7 and 15 years in whom the symptoms at the onset were delirium and extreme excitement which in the older girl were preceded by a stage of torpor suggesting coma. Meningitis was suggested, but the spinal fluids were practically normal. The signs of pneumonia appeared, clearing up the diagnosis, and both patients recovered. He noted that these brain disturbances may take the form of convulsions, delirium or most

82. Blauner, S. A.: Physical Signs of Pneumonia in Children, New York M. J. **112**:1032 (Dec. 25) 1920.

83. Gunewardene, H. O.: Central Pneumonia in a Child of Two, *Lancet* **2**: 73 (July 10) 1920.

84. Nobécourt, P.: The Brain and Meninges in Pneumonia in Children, *Bull. méd., Par.* **35**:209 (March 12) 1921. *Abstr. J. A. M. A.* **76**:1281 (April 30) 1921.

frequently somnolence which may come with the rise of temperature. Extreme general hyperaesthesia and ocular disturbances are frequent. The outlook is somewhat serious even with a serous meningitis, and of course grave with purulency. He stated that the treatment must be prompt and vigorous, being to relieve congestion of the nerve centers as by hot baths or packs every four to six hours. Lumbar puncture should be done once anyway if it is a serous meningitis, repeatedly, if a purulent meningitis.

Sequels and Complications.—Overend⁸⁵ made a plea for the more frequent radiologic examination of the chest in children, particularly in those who fail to recover completely after pneumococcal infections of the lungs. He stated that many cases of ill health in children after pneumonia and other infectious diseases are due to unresolved pneumonia produced by a chronic pneumococcal infection and are not tuberculous. Bronchiectasis is likely to follow attacks of chronic or indurative basal pneumonia; disseminated patches of bronchopneumonia are more liable to produce areas of diffuse bronchial dilatation.

Packard⁸⁶ drew attention to the fact that because of the recent high incidence of pneumonia, a great many chronic lung changes will be encountered in the next few years. He felt that with due allowance for the normal variations in children, abnormal physical signs at one apex should be considered as due to pulmonary tuberculosis until proved not to be, while those at the base should be looked on as nontuberculous until definitely proved otherwise.

In a paper on chronic nontuberculous lung infection, Field⁸⁷ reviewed the literature on this condition and emphasized its diagnostic features. Cases with chronic cough which is not paroxysmal, purulent sputum which is persistently negative for acid-fast bacilli, insignificant radiologic findings with râles located in the lower half of the chest (in the absence of a heart lesion), and the general health only slightly impaired, these, he said, are undoubtedly cases of chronic nontuberculous lung infection.

Radin⁸⁸ described twelve cases of chronic lung disease following the influenza epidemic, in all of which the pathologic process was at the base of the lungs, except in three cases which proved to be tuberculous. Sputum was absent in the pleuritis cases as a general rule but was copious in the bronchitis cases. Improvement was the rule, but slow.

85. Overend, W.: Basal Pneumonic Residues in Children, *Tubercle* **1**:547 (Sept.) 1920.

86. Packard, E. N.: Nontuberculous Lung Changes Following Pneumonia, *J. A. M. A.* **75**:1537 (Dec. 4) 1920.

87. Field, C. G.: Chronic Nontuberculous Lung Infection, *Am. J. M. Sc.* **159**:442 (March) 1920.

88. Radin, M. J.: Chronic Lung Disease Following the Influenza Pandemic of 1918-1919, *Am. J. M. Sc.* **160**:233 (Aug.) 1920.

Several apparently unusual complications have been reported. Fleischner's⁸⁹ patient apparently inhaled some sand, and developed a bronchopneumonia. On the eighth day, his heart was noted as markedly displaced to the right, the cause not being made out until six days later when an extensive subcutaneous emphysema appeared beginning in the right supraclavicular space. It was thought that the cardiac displacement was due to an extensive mediastinal emphysema since at no time could a pneumothorax be detected. Thomas and O'Hara⁹⁰ reported a case of pneumococcus Type I vegetative endocarditis following lobar pneumonia, and felt that there is some cause for believing that the Type I organism is mainly responsible for pneumococcus endocarditis.

Kerr⁹¹ considered that acute gastric dilatation is a positive danger to the child's life in one out of every four cases of lobar pneumonia. The first symptoms of this complication are usually those of restlessness accompanied by an increased thirst and vomiting. Acute epigastric pain may or may not be in evidence. The respirations are either increased or the breathing much more embarrassed, and there is every evidence of increased exhaustion including cyanosis. These symptoms, however, are inconstant. Examination often reveals a visible and palpable tumor in the upper abdomen. Usually after the first few hours, the pinched features and the objective evidences of circulatory shock are marked. The treatment of this condition must be prompt. If the fluid content of the stomach is marked, Kerr said to place the patient on the left side of the chest anteriorly, and raise the foot of the bed; then perform an efficient lavage; and then withhold everything by mouth at least twelve hours.

In a discussion of the abdominal reflexes in pneumonia, Pastore⁹² referred not to those cases wherein the abdominal symptoms usher in pneumonia in children, and subside as the pneumonia becomes installed, but to those in which appendicitis is simulated as a complication of pneumonia, or actually exists as such a complication. The practitioner must keep his eye on the lung in appendicitis and on the appendix in pneumonia.

89. Fleischner, E. C.: Heart Displacement Apparently Due to Mediastinal Emphysema Following Aspiration Pneumonia, *Am. J. Dis. Child.* **21**:206 (Feb.) 1921.

90. Thomas, H. M., Jr., and O'Hara, D.: Pneumococcus Type I Vegetative Endocarditis: Report of a Case Following Lobar Pneumonia, *Johns' Hopkins Hosp. Bull.* **31**:417 (Nov.) 1920.

91. Kerr, LeG.: The Mortality Factors of Lobar Pneumonia in Children, *New York State J. M.* **20**:348 (Nov.) 1920.

92. Pastore, S.: Abdominal Reflexes with Pneumonia, *Policlinico* **27**:1406 (Dec. 6) 1920. *Abstr. J. A. M. A.* **76**:276 (Jan. 22) 1921.

In his study of pneumococcus peritonitis in infancy and early childhood, Beaven⁹³ concluded that this disease is in the great majority of cases preceded by pulmonary involvement, either as pneumonia or as empyema.

Nobécourt and Mathieu⁹⁴ discussed purpura occurring in pneumococcus infections of lung, intestines or meninges, and stated that the eruption is evidently an expression of septicemia, and indicates a grave prognosis.

Treatment: Isolation.—Southworth⁹⁵ considered the isolation of pneumonia cases of sufficient importance to make a plea for it the main theme of his president's address read before the American Pediatric Society in May, 1920.

Locke, Thomas and O'Hara,⁹⁸ reported in detail for the pneumonia service of the Boston City Hospital. They believed the advantages of a separate pneumonia service in a hospital include the following: The segregation of pneumonia cases greatly diminishes the danger of infection to other patients in the hospital. A separate pneumonia service facilitates the attainment of the particularly careful observation and nursing which is necessary, and also it enables the resident physicians to acquire the expert training and experience which is necessary for certain forms of treatment. Such a service also facilitates the routine special technical study required for the proper treatment of these cases, as well as research study and instruction.

Serum.—In a series of short articles on biologic therapy, the use of antipneumococcus serum was discussed by Cole.⁹⁶ Inasmuch as the pneumococci of Types I, II and III have immunologic properties of great specificity, an immune serum that will protect mice against lethal doses of any strain of pneumococci of one type will do so for all strains of that same type, but not of the other types. Consequently an immune serum has therapeutic value in man only against the strains of its particular type. The various strains in Type IV possess too high a degree of individual specificity to make an immune serum for Type IV practicable. Therapeutically effective immune serums for Types III and II have not yet been developed. But the serum of horses immunized to Type I pneumococci is of such great value in the treatment of cases of pneumonia due to Type I pneumococci, that all cases of pneumonia should be typed at once so that this serum can be used in the treatment of these cases of Type I origin. The dose of the

93. Beaven, P. W.: Pneumococcic Peritonitis in Infancy and Early Childhood, *Am. J. Dis. Child.* **20**:341 (Oct.) 1920.

94. Nobécourt, P., and Mathieu, R.: Purpura in the Pneumococcal Infections of the Breastfed, *Arch. de méd. d. enf.* **23**:689 (Dec.) 1920.

95. Southworth, T. S.: Segregation of Pneumonia, *J. A. M. A.* **75**:919, (Oct. 2) 1920. Also abstr. *Arch. Pediat.* **37**:666 (July) 1920.

96. Cole, R.: Antipneumococcus Serum, *J. A. M. A.* **76**:111 (Jan. 8) 1921.

serum is from 90 to 100 c.c., given intravenously, repeated every eight hours until the infection is overcome. The average total dosage is from 200 to 300 c.c., but in severe cases a total of 1,000 c.c. may be necessary. Cole added that in 495 cases of lobar pneumonia due to Type I pneumococci and treated with immune serum, there was a mortality of only 10.5 per cent.

In experimental pneumococcus Type I pneumonia in monkeys, as investigated by Cecil and Blake,⁹⁷ the intravenous injection of Type I pneumococcus serum exercises a specific therapeutic effect, frees the blood promptly and permanently from pneumococci, shortens the course of the disease and greatly moderates its severity. The earlier the serum is administered the shorter and less severe the pneumonia. Frequent injections are also a factor in obtaining favorable results. When serum treatment is instituted late in the disease, the injections must usually be continued over a longer period of time in order to achieve success.

Locke, Thomas and O'Hara⁶⁸ reported that they had had good results with the Rockefeller Institute method of using antipneumococcus serum for Type I cases, particularly when given early, and also particularly when there was a marked thermal reaction. Cecil⁹⁷ gave a clear and instructive presentation of this serum treatment, and he also urged⁶⁴ that the bacteriologic diagnosis of each case be made early not only to determine whether or not to use serum treatment but also for prognostic value. Niles⁹⁸ felt that no patient suffering with lobar pneumonia can be said to have been given his maximum chances for recovery unless the type of infecting organism has been determined and if this proved to be Type I pneumococcus, to have received adequate doses of serum. The exceptions are: (1) young children whose intoxication is mild and in whom the difficulty of treatment is great; (2) adults first seen late in the disease, who are but mildly intoxicated and showing improvement, and (3) elderly patients. He urged that the serum reach the vein warmed to body temperature. Antipneumococcus serum used in the treatment of pneumococcus pneumonia in three infants of two, four, and five months of age, made a very favorable impression on Nobécourt and his associates.⁷¹

Gray⁹⁹ made use of Kyes' antipneumococcus serum, a serum supposedly of high antibody content, achieved by using an insusceptible host, the barnyard fowl, thereby allowing the use of unusually large

97. Cecil, R. L.: The Prevention and Serum Treatment of Lobar Pneumonia, *M. Clinics N. America* **4**:191 (July) 1920.

98. Niles, W. L.: The Serum Treatment of Lobar Pneumonia, *New York M. J.* **113**:871 (June 15) 1921.

99. Gray, A. W.: Antipneumococcus Serum (Kyes's) in the Treatment of Pneumonia, *Am. J. M. Sc.* **159**:885 (June) 1920.

numbers of virulent living pneumococci as antigen. As a result, the dosage of this serum was only from 2.5 to 10 c.c., given intravenously every day or two, and totalling from 60 to 90 c.c. in the cases of recovery. With this method, Gray had a mortality of 16.7 per cent. in 234 serum treated cases of pneumococcus pneumonia in soldiers and a mortality of 53.6 per cent. in 1,684 similar cases at the same time, treated in exactly the same manner except that they received no serum. No mention is made of the types of pneumococcus. However, Gray added that the *modus operandi* of the serum is, of course, of great interest but except for the fact that the serum is antibacterial, any statement would be hypothetical. He felt that the therapeutic value of any treatment must finally be judged by its reduction of mortality.

Management and Drugs.—Heiman¹⁰⁰ made a study of pneumonia in infancy and childhood, and since his mortality rate in the bronchopneumonia cases in children under one year was but 22.9 per cent., his method of treatment is of interest. He emphasized the necessity of hygienic care and efficient nursing, especially to prevent infection of the skin, eyes and mouth. Cold air treatment was not favored for any type of case. Diluted milk, gruel, fruit juices and an abundance of water form the chief elements of the food. Milk of magnesia in the morning and an enema by night are routine for purposes of elimination.

Aromatic spirits of ammonia and liquor ammonii anisatus are useful for mild stimulation and seldom upset the stomach. He also felt that whisky in doses of from 10 to 20 drops at four hour intervals helps in producing temporary stimulation and in its caloric value, and given this way has no subsequent depressing effect. Warm packs are useful in the moderately severe cases.

He did not look with favor on dry cupping and digitalis. The latter had been used in a considerable number of cases without any appreciable beneficial results, since as a rule the pulse was not lowered nor the blood pressure raised by this agent.

On the other hand, Eggleston¹⁰¹ has found that in the absence of satisfactory therapeutic response, one can be certain that digitalis has been given a fair trial only when it has been administered to the point of production of one or more of the criteria of minor intoxication. Freeman¹⁰² also said, in discussing Heiman's paper, that though for years he did not use digitalis in children, recently he had seen it do a

100. Heiman, H.: A Study of Pneumonia in Infancy and Childhood During Recent Epidemics, *Am. J. Dis. Child.* **20**:119 (Aug.) 1920.

101. Eggleston, C.: Some Newer Concepts in Digitalis Therapy, *Am. J. M. Sc.* **160**:625 (Nov.) 1920.

102. Freeman, R. G.: quoted by L. C. Schroeder in private notes.

great deal of good and he had been using it in large doses, and had found it valuable especially when given early to older children.

Brooks and Carroll¹⁰³ made a special plea for the proper management of the heart in pneumonia, believing that the most frequent immediate cause of death in all types of pneumonia is cardiac failure, which, in turn, is usually due to a deficiency of the right side of the heart. This deficiency occurs because of the very limited muscle reserve capacity of the right side of the heart, and also because of a myocardial degeneration, the result of the toxemia. They believe that small doses of digitalis at the outset of a pneumonia enable the right side of the heart to realize in the presence of an initial increased pulmonary pressure, a compensatory circulatory adjustment. Accordingly, they give the tincture of digitalis when the diagnosis is first made, or even suspected.

Meakins¹⁰⁴ and Rudolph,¹⁰⁵ both advocated the administration of oxygen for the relief and prevention of anoxemia and its attendant cyanosis, in cases of pneumonia. The former used the Haldane face-mask attachment for the administration of the oxygen in satisfactory concentration, whereas Rudolph administered the gas through a rubber tube inserted into one nostril, using rhythmical compression of the opposite nostril during inspiration, the patient's mouth, of course, being kept closed.

Lassalle¹⁰⁶ advocated the subcutaneous injection of 1 c.c. of ether every four hours, or twice a day, the earlier in the disease the better, believing that the action of the ether is anti-infectious, antithermic, antispasmodic and cardiotonic. He had never witnessed any injurious by-effects in over 200 injections.

In ninety infants with pneumonia or capillary bronchitis, Vogl¹⁰⁷ made subcutaneous injections of 0.2 c.c. of a 1:1,000 solution of epinephrin with what he considered were excellent results. He believed the treatment to be logical in that it combatted the process of exudation in the finer air passages, and the infiltration of the lung tissue.

In his treatment of a case of central pneumonia in a child of 2 years, Gunewardene⁸³ noted benefit from aspirin and later from strychnine.

103. Brooks, H., and Carroll, J.: The Management of the Heart in Pneumonia, *Am. J. M. Sc.* **160**:815 (Dec.) 1920.

104. Meakins, J. C.: The Therapeutic Value of Oxygen in Pulmonary Lesions: Preliminary Note, *Brit. M. J.* 324 (March 5) 1920.

105. Rudolph, R. D.: The Therapeutic Use of Oxygen, *Am. J. M. Sc.* **160**:542 (Oct.) 1920.

106. Lassalle, M.: A Contribution to the Study of Bronchopneumonia in Infancy and to Its Treatment, *Arch. de méd. d. enf.* **23**:414 (July) 1920.

107. Vogl, J.: Epinephrin in Pneumonia in Infants, *Arch. f. Kinderh.* **68**:215 (Oct. 16) 1920. *Abstr. J. A. M. A.* **75**:1682 (Dec. 11) 1920.

John,¹⁰⁸ in a description of his routine administration of glucose in pneumonia, advocated giving intravenously 250 c.c. of a 10 per cent. aqueous solution of glucose two or three times a day. He further advised the administration in the glucose solution of the various medicines needed, so that the solution usually given consists of: Tincture digitalis, 7; morphin sulphate, 0.008; atropin sulphate, 0.00064; glucose, 10 per cent. solution, 250, heated to 50 C. The administration should take from fifteen to thirty minutes. The morphin and atropin are to secure rest and also to prevent the chills which sometimes follow any intravenous medication.

Rathery and Bonnard¹⁰⁹ have treated cases of bronchopneumonia of the lower and middle lobes by injecting through the tissues of the neck into the trachea from 5 to 10 c.c. of 10 per cent. gomenol oil. They pass the needle in immediately above the cricoid cartilage in the midline. They stated that the results have been excellent, the injections giving immediate relief to the dyspnea, and a quick change in the state of general wellbeing. They have not had an opportunity of using this method in the treatment of bronchopneumonia of the apices.

Brooks¹¹⁰ called attention to the duty of the physician not to neglect his pneumonia patients when the temperature has returned to normal, nor even when they are up and about. He considered that the physician's responsibilities and liabilities cease only when the physician has returned his patient to his usual life requirements in as normal and efficient a condition as it is possible to gain. Brooks discussed diet, hygiene and graded exercises, as well as the possible complications and sequels that might appear.

Vaccines.—Cecil¹¹¹ described the preparation, method of administration, dosage, reactions, indications for use, and contraindications for pneumococcus vaccine. He believed that prophylactic vaccination against pneumonia using a mixed saline vaccine of pneumococci Types I, II and III, to be of marked advantage where large groups of individuals are living together under abnormal conditions as in army encampments. But he advised the use of the greatest caution in recommending the treatment of pneumonia by vaccines of whatever modification, until such time as the value of these vaccines for this purpose may be confirmed by large and well controlled series of cases. He and Blake found that the subcutaneous inoculation of monkeys with pneumococcus Type I vaccine in doses comparable with those

108. John, H. J.: Glucose as an Adjunct Measure in the Therapy of Pneumonia, *Am. J. M. Sc.* **160**:542 (Oct.) 1920.

109. Rathery, F., and Bonnard: Intratracheal Medication in Acute Bronchopneumonia, *Bull. et mém. Soc. méd. d. hôp. de Par.* **44**:63 (Jan. 16) 1920.

110. Brooks, H.: The Management of Convalescence in Pneumonia, *M. Clinics N. America* **4**:1423 (March) 1921.

111. Cecil, R. L.: Pneumococcus Vaccine, *J. A. M. A.* **76**:178 (Jan. 15) 1921.

employed in man, does not protect them against subsequent attacks of pneumococcus Type I pneumonia, either spontaneous or experimental. Vaccination did, however, modify the course of the disease. Invasion of the blood stream by the pneumococci in vaccinated animals is usually slight, and the proportion of recoveries is considerably higher for vaccinated than for unvaccinated monkeys.

Howell¹¹² experimented with the army lipovaccine, and found apparently that immune bodies appearing after the injection of lipopneumococcus vaccines develop slowly, not reaching their height for a considerable time, and that they persist for a duration of at least several months. She further found that agglutinins, complement fixing bodies, and protective bodies for pneumococci Types I, II and III are demonstrable in the serum of individuals vaccinated with pneumococcus lipovaccine. These antibodies appear in the serum rather late and are present to some degree for at least one year.

Conclusion.—In discussing the change of type of disease, Rolleston¹¹³ noted from the clinical viewpoint how various diseases had changed their types from one period to another, notably influenza, pneumonia and scarlet fever, and that causes for these alterations in the clinical features were appearing in modern scientific knowledge, such as the appearance of the pneumococcus and *Streptococcus hemolyticus* in measles and influenza, and the discovery of the different types of pneumococci. He believed also that changes in the resistance of the patients were important.

EMPHYEMA

Pathogenesis.—Moschcowitz¹¹⁴ wrote a long and elaborate but excellent paper on the newer conceptions of the pathogenesis and treatment of empyema. As to the pathogenesis, he concluded that empyema in most instances results from the rupture of a small subpleural pulmonary abscess, and is in itself the final stage of a process in which the first stage is a serous pleurisy, and the second a seropurulent pleurisy. This latter is the so-called formative stage of an empyema, and is unaccompanied by pleural adhesions, while the stage of final empyema is always accompanied by adhesions. In fact, the vast majority of empyemas are of the encapsulated variety, and very few occupy the entire pleural space. He also concluded that metastatic

112. Howell, K. M.: Blood Changes and Antibody Production in Human Beings after Injection of Pneumococcus Lipovaccine, *J. Infect. Dis.* **27**:557 (Dec.) 1920.

113. Rolleston, H.: The Change of Type of Disease, *J. A. M. A.* **74**:1495 (May 29) 1920.

114. Moschcowitz, A. V.: Newer Conceptions of the Pathogenesis and Treatment of Empyema, *Am. J. M. Sc.* **159**:669 (May) 1920.

suppurations accompanying empyemas are to be found rather as complications of the causative pneumonia than of the empyema.

Renaud¹¹⁵ wrote that acute purulent pleurisy is always the reaction of the pleura to some lesion in the lung. The nature and the distribution of the pulmonary lesion are what determine the pleurisy, and the prognosis depends on the process in the lung.

Graham¹¹⁶ made a study of the influence of respiratory movements on the formation of pleural exudates, having clinically observed the appearance of a pleural exudate of 1,000 c.c. or more in two days' time after the onset of a streptococcal bronchopneumonia. He experimented with dogs' lungs suspended in a closed bell jar, the trachea being connected by a tube with the atmosphere. He produced expansion and contraction by varying the air pressure in the jar, and noted the formation of an exudate from the surface of the lungs. He explained the exudation during inspiration as due to suction outside the visceral pleura, and during expiration as due to pressure squeezing fluid out of an oedematous pleura, there being a sudden diminution of the lung surface in expiration.

Occurrence.—Of the 1,869 cases of pneumonia admitted to the Babies Hospital in New York City in the seven years prior to Jan. 1, 1920, Spence¹¹⁷ found that 204 cases, or approximately 11 per cent., either had empyema at the time of admission or developed it during the stay in hospital. All his cases of empyema were the sequel of pneumonia. Glenn¹¹⁸ in her series of sixty-four cases of empyema in children under 12 years of age noted a greater incidence in males than in females (44 to 20). She also believed that the left side is more often involved than the right, her figures in this respect being 34 to 23, and the corresponding figures of Ladd and Cutler,¹¹⁹ (95 to 73, with 4 bilateral) are in apparent accord. Hand¹²⁰ spoke of the rarity of empyema in colored children.

Symptomatology and Diagnosis.—Spence¹¹⁷ believed the most important physical signs of fluid in the pleural cavity of the young child are flatness on percussion and displacement of the heart. The

115. Renaud, M.: The Treatment of Acute Purulent Pleurisy, *Bull. et mém. Soc. méd. d. hôp. d. Par.* **44**:1225 (Oct. 15) 1920; **44**:1251 (Oct. 29) 1920; **44**:1334 (Nov. 12) 1920.

116. Graham, E. A.: Influence of Respiratory Movements on the Formation of Pleural Exudates, *J. A. M. A.* **76**:784 (March 19) 1921.

117. Spence, R. C.: Empyema in Infants and Young Children, *Am. J. Dis. Child.* **20**:545 (Dec.) 1920.

118. Glenn, E.: Empyema in Children: Report of 64 Consecutive Cases, *New York M. J.* **112**:987 (Dec. 18) 1920.

119. Ladd, W. E., and Cutler, G. D.: Empyema in Children, *Am. J. Dis. Child.* **21**:546 (June) 1921.

120. Hand, A.: The Diagnosis of Empyema in Children, *Pennsylvania M. J.* **23**:697 (Sept.) 1920.

degree of leukocytosis is no guide to either the diagnosis or the prognosis, he found. Wilcox⁸⁰ wrote that dullness or dull tympany and sharp bronchial breathing and voice sounds are found over pleuritic effusion in childhood when that effusion is in sufficient quantity to exert pressure on the adjacent lung and produce tension in the thin chest wall. Hand¹²⁰ noted that there was no one pathognomonic sign of empyema in children. He called attention, however, to the differences in the physics of the child's chest as compared to that of the adult, viz., the greater resiliency of the walls, the greater mobility of the heart, and the greater ease with which the vocal and respiratory sounds may be transmitted through effusions.

Blauner⁸² found that because of the great resiliency of a child's lung, the physical signs of compression of the lung usually found in empyema, such as bronchial breathing, may be absent. In one paper Foster⁶⁶ discussed in detail the diagnosis of empyema, and disagreed with the teaching that there is always a displacement of neighboring viscera, such as of the heart or liver. In another,¹²¹ he stated that the indications of empyema are not in signs alone at best, but in the evidence of a persistent infection, accompanied by signs in the chest which might be due to a pleural abscess.

In a child of two and a half years, Zuviria¹²² found normal percussion resonance with ordinary percussion, but when the percussion was extremely gentle and the child sitting up without support except for its hands, dullness was found on the entire left side of the chest, and puncture in the ninth interspace released an effusion. The coexistence of a vesicular murmur was misleading at first.

Wessler¹²³ gave a number of case reports and roentgen-ray illustrations of several different varieties of encapsulated empyemata, including some particularly clear illustrations of interlobar effusions. He stated that the clinical diagnosis of encapsulation is best made when based on a consideration of all the symptoms and physical signs, though in a few cases there may be found physical signs of direct applicability.

Treatment.—Moschowitz¹¹⁴ believed that the treatment of an empyema should be begun in the formative stage before the exudate has been converted into frank pus. He wrote that it is unwise to perform an operation in this formative stage. The mortality is terrific because the accompanying pneumonia is still in full bloom, and furthermore, because of the absence of adhesions there occurs a pneumothorax with "fluttering of the mediastinum" and consequent embarrassment of

121. Foster, N. B.: The Complications of Pneumonia, *Med. Rec.* **99**:950 (June 4) 1921.

122. Martinez, Zuviria, E.: *Prensa med., Argentina* **6**:195 (Dec. 10) 1919.

123. Wessler, H.: The Diagnosis of Encapsulated Pleural Effusions, *M. Clinics N. America* **4**:69 (July) 1920.

the heart action. He felt that the best surgical procedure in this stage is repeated aspirations, done every twelve to twenty-four hours, in order to relieve the respiratory embarrassment due to the mechanical pressure of the rapidly accumulating fluid. He added that in a few cases this measure is curative. McCrae¹²⁴ also made a plea for the early aspiration of any pleural effusion occurring in lobar pneumonia in order to prevent, if possible, the formation of an empyema subsequently. A number of other authors, Ladd and Cutler,¹¹⁹ Lowenburg,¹²⁵ Ransohoff,¹²⁶ Renaud,¹¹⁵ and others, called attention strongly to the dangers of early operation for empyema, and particularly in the presence of a pneumonia. Foster⁶⁶ believed that aspiration can be continued and operation postponed as long as the patient shows improvement, as by better appetite and sleep, a lower fever and pulse rate, and other evidences of diminished infection, such as less sweating, and an improvement in the patient's sense of well being and strength. Hodge¹²⁷ also wrote in similar strain, and Renaud¹¹⁵ considered the pleural complication as negligible in comparison to the condition of the lungs and heart.

Spence¹¹⁷ quoted Swift as advising early operation as soon as the diagnosis has been made, since in his experience all cases in which a pleural exudate containing bacteria was obtained, ultimately came to operation. This has not been Spence's experience with infants and young children at the Babies Hospital, where in six cases, although a seropurulent fluid containing many pneumococci was obtained in small amount by aspiration, all recovered without further aspiration. However, Spence found a high net mortality rate for those cases that were treated only by aspiration since this was the only operative procedure used for the cases received in a nearly moribund condition. In this same connection but in soldiers, Abrahams⁷⁸ reported very remarkable results. In 116, or 20.8 per cent., of his cases of untyped lobar pneumonia, empyema was considered present, but aspiration was done freely and empyema diagnosed even if only a little thin serous effusion containing few pus cells was obtained. Resection was done in only thirty of the 116 cases, the other eighty-six being all successfully treated by aspiration only, although sixty showed thick pus, including twenty-four in which either pneumococci or streptococci were found. However, twenty-three deaths occurred among the thirty who were operated on.

124. McCrae, T.: The Treatment of Empyema in Lobar Pneumonia by Early Aspiration, *Canad. M. A. J.* **10**:162 (Feb.) 1920.

125. Lowenburg, H.: Pleural Disease in Infants and Children. With Special Reference to Empyema, *New York M. J.* **112**:124 (July 24) 1920.

126. Ransohoff, J.: Empyema at the Cincinnati General Hospital During the Influenza Epidemic, *J. A. M. A.* **74**:238 (Jan. 24) 1920.

127. Hodge, E. B.: Empyema in Children, *Arch. Pediat.* **38**:18 (Jan.) 1921.

As for the actual aspiration, when exploratory, Hand's¹²⁰ site of choice was the sixth interspace in the midaxillary line, preferably with the patient under general anaesthesia. After inserting the needle, he advocated in turn exploring inwards, backwards, and forwards, with only one insertion of the needle.

That thoracentesis is not entirely without danger was shown by Schlaepfer¹²⁸ who reported an instance wherein, during this operation, the needle being used for the exploratory puncture was left open as the syringe was removed. Air was aspirated and apparently drawn into a vein in the lung, for air embolism in the brain resulted, shown by loss of consciousness for 2½ hours, and total blindness for three days. He believed that air aspiration and embolism may explain many of the cases recorded as pleural shock, although in other instances slight shock on a nervous basis in the predisposed may be assumed.

An editorial¹²⁹ in the JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION called attention to the possibility of a tiny droplet of air passing through a hollow needle into a pulmonary vessel during thoracentesis, and thence to a cerebral vessel causing grave symptoms, even death. It cautioned the operator to avoid this danger as by connecting the needle to rubber tubing and filling this system with saline solution.

Apert and Vallery-Radot¹³⁰ reported an instance of sudden death during thoracentesis in a 4 year old boy who was terribly frightened and violently resisted the puncture which had to be done twice while the patient was firmly held by a nurse. Fatal syncope suddenly occurred. At necropsy, a myocarditis was found which was thought to have been diphtheritic since any other kind in a child of four is rare. The boy had been sick a month, and had developed a bilateral serous effusion, but there were no symptoms suggestive of diphtheria.

Villandre¹³¹ believed that before operating in a case of purulent pleurisy, a great deal more attention should be paid to the bacteriology than is usual. He felt that the pneumococcus cases may, but the streptococcus cases always require incision, the latter almost always requiring in addition the use of surgical solution of chlorinated soda, or of an antiseptic vapor, for the best results. He presented an excellent description of the various methods of treatment. Foster¹²² spoke of

128. Schlaepfer, K.: A Case of Three Days' Blindness after Diagnostic Puncture of the Lung, *Deutsch. Ztschr. f. Chir.* **159**:132 (Sept.) Abstr. *J. A. M. A.* **76**:828 (March 19) 1921.

129. Editorial: Air Embolism Following Thoracentesis, *J. A. M. A.* **76**:1314 (May 7) 1921.

130. Apert, and Vallery Radot, P.: Sudden Death During Puncture of Pleura in a Child of 4 years. Myocarditis, *Bull. et mém. Soc. méd. d. hôp. de Par.* **44**:852 (June 18) 1920.

131. Villandre, C.: The Treatment of Acute Purulent Pleurisy, *Bull. méd. Par.* **34**:87 (Jan. 31) 1920.

the danger of early operation in streptococcus empyema, and thought it better to aspirate as long as this procedure gave improvement in symptoms. He felt, however, that often a pneumococcus empyema was benefitted by early operation. Spence¹¹⁷ noticed that when the pus yielded a pure culture of pneumococcus, the mortality was lowest; but when there was a mixed infection or a pure growth of streptococcus, the mortality was highest.

Spence further noted that the length of time since the onset of symptoms also seemed of importance in the prognosis. If short, the mortality was high from overwhelming or virulent infection; if from two to six weeks, the mortality was lowest; if over six weeks, the mortality was again high from neglect or complications. Locke¹³² called attention to the fact that the earlier the empyema occurred in the course of a pneumonia, the worse was the prognosis. Also, the prognosis of empyema with lobar pneumonia is much more favorable than with bronchopneumonia. Glenn¹¹⁸ thought that when the patient is operated on within the first week after the onset, the average stay in the hospital is shorter and the proportion of cures higher than in those operated on at the later time.

Operative Treatment.—A detailed review of the literature on this branch of the subject is not indicated at this time. Accordingly only a few points from various of the papers will be noted here.

Moschcowitz¹¹⁴ stated that the treatment in the acute stage of an empyema consists of a simple intercostal thoracotomy, an operation which need not be considered urgent, and which should be performed when the patient's condition is otherwise perfectly satisfactory. Urgent thoracotomy is indicated only in acute pyopneumothorax. He felt that the Carrel-Dakin treatment, properly carried out, has proved of superlative value in the postoperative treatment of empyema and should be used in every case. There are no contraindications to its use, and the mortality of acute empyema treated by these methods is lower than that reported by other methods of treatment, he found. Empyema cavities heal by three methods: (1) by the formation and absorption of a sterile exudate; (2) by the formation and "absorption" of a closed pneumothorax, and (3) by the "classical" method, i. e., the expansion of the lung and obliteration of the pleural cavity by adhesions. Chronic empyema should not occur, or at least should become very rare, if the methods of treatment of acute empyema formulated above are practised. Wilensky¹³³ wrote in much the same strain. Ransohoff¹²⁶ felt that flushing of the cavity with surgical solution of chlorinated

132. Locke, E. A.: Empyema Complicating Pneumonia, *M. Clinics N. America* **4**:471 (Sept.) 1920.

133. Wilensky, A. O.: Present Status of Empyema, *Am. J. M. Sc.* **160**:384 (Sept.) 1920.

soda or other solution is unnecessary, except when defervescence does not occur, indicating that spontaneous sterilization of the cavity is not progressing normally. He thought that operation not earlier than the end of the second week gave the best results, and that rib resection is indicated only when sufficient space is not at command without it. He favored some type of the occlusion method of operation by which the entrance of air into the pleural cavity is prevented and the exit of pus facilitated. A suction apparatus attached to the tube was deemed unnecessary. Spence¹¹⁷ stated, however, that in the experience of the Babies Hospital, siphon drainage has given better results in the treatment of empyema in infancy than any other treatment employed.

Ladd and Cutler¹¹⁹ remarked that whereas children do not stand rough handling and hemorrhage as well as adults, the lung can be freed gently, sufficiently to allow it to expand without causing marked bleeding. In the streptococcus infections, these authors felt that aspiration or closed drainage through a tube would probably supply sufficient drainage and result in a lowered mortality. In cases of pneumococcus empyema, they considered closed drainage useful as a temporary measure for the extremely sick patients, but not to be recommended as the operation of choice. It does not supply adequate drainage nor allow the operator to free the lung which can be done in a child through a small opening with one finger. They considered the cause of collapsed lung to be not the presence of atmospheric pressure through an open wound, but the result of inadequate operation and drainage.

Rosenberg¹³⁴ recommended the open pleura puncture of Schmidt in cases in which the exudate extends beyond the upper third of the scapula or when no resorption takes place after two or three weeks. The method consists mainly in replacing the exudate with air, thereby preventing the redevelopment of exudate and the formation of broad adhesions between the costal and visceral pleura.

Morrison¹³⁵ reported a case of a 2½ year old girl with a left-side Type I pneumococcus empyema following lobar pneumonia, but complicated by whooping cough. Under procain local anesthesia, he resected part of the eighth rib through an incision made over the ninth rib, believing that an indirect opening into the pleural cavity is much better than a direct one in that it prevents air rushing in and out of the pleural cavity with each respiration. A valve fashioned from the soft tissues themselves is more efficient than any mechanical valve, and he also considered that general anaesthetics are contraindicated. In

134. Rosenberg, M.: Exudative Pleurisy, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **32**:267, 1920. *Abstr. J. A. M. A.* **75**:1684 (Dec. 11) 1920.

135. Morrison, W. R.: Acute Empyema Complicated by Whooping Cough, *Boston M. & S. J.* **184**:307 (March 24) 1921.

another article¹³⁶ he gave a more detailed description of the operative technic of this operation.

Moschcowitz¹¹⁴ considered that feeding with a diet rich in calories was a valuable adjuvant in the treatment particularly of the formative stage. Locke¹³² also laid stress on the necessity of giving consideration to the diet in order to avoid, if possible, the rapid and marked emaciation which is so common in empyema, and he urged that the patient be encouraged to take a special dietary having a fuel value of from 3,000 to 3,500 calories. He also advocated the open air treatment whenever possible. Hodge¹²⁷ called attention to the value of blowing exercises started as early as possible in order to expand the lung.

Gay and Morrison¹³⁷ experimented with various dye stuffs in the treatment of experimental streptococcus empyema in rabbits, and stated that their results did not justify the anticipation of practical therapeutic results from the use of dye stuffs in empyema due to the streptococcus. They added, however, that they have not as yet considered the possibilities of using dyestuffs combined with metallic compounds such as with mercury. Gay and Stone¹³⁸ made elaborate experiments on animals with a strain of streptococcus isolated from a case of human empyema, and concluded that preventive vaccination against human streptococcus empyema was not practicable, and that therapeutic results in animals with such vaccines were consistently negative. On the other hand, Dufour and Debray¹³⁹ reported the recovery from a streptococcus purulent pleurisy under the influence of vaccine therapy alone, of a girl of 15 in whom the disease had developed slowly and the general health was good.

After a study of twenty-two cases of pneumococcus empyema in children with particular reference to demonstrable precipitins in the exudate, Floyd¹⁴⁰ suggested that pleural irrigation with an appropriate immune serum be used as a means of treatment of this disease in order to increase locally the immune substances that tend to limit the duration of the disease. He further noted that the pleura will clear itself of

136. Morrison, W. R.: The Surgical Treatment of Acute Empyema by Valve Drainage, Provided by Flap of Skin, Fascia and Muscle, under Local and Paravertebral Anaesthesia, Boston M. & S. J. **182**:366 (April 8) 1920.

137. Gay, F. P., and Morrison, L. F.: Experimental Streptococcus Empyema: II. Attempts at Dye Therapy, J. Infec. Dis. **28**:1 (Jan.) 1921.

138. Gay, F. P., and Stone, R. L.: Experimental Streptococcus Empyema: Attempts at Prevention and Therapy by Means of Vaccines and Serum, J. Infec. Dis. **26**:265 (March) 1920.

139. Dufour, H., and Debray: Vaccine Treatment of Purulent Pleurisy, Bull. et mém. Soc. méd. d. hôp. de Par. **45**:16 (Jan. 14) 1921. Abstr. J. A. M. A. **76**:896 (March 26) 1921.

140. Floyd, C.: A Study of the Precipitin Test in Cases of Pneumococcus Empyema, J. Immunol. **5**:321 (July) 1920.

a pneumococcus infection in a much shorter time than the average if the secondary invaders can be excluded.

Chronic Empyema.—Cauchoux¹⁴¹ stated the causes of chronic empyema to be (1) incomplete drainage; (2) the presence of a foreign body; (3) the presence of an osteitis of a rib, and (4) other conditions, often undeterminable. He studied the various ways of treating this form of the disease, and believed that much help can be obtained from the use of irrigation with surgical solution of chlorinated soda. Moschowitz¹⁴² stated that chronic cases of empyema may be defined as such which are not amenable to treatment by the Carrel-Dakin method, but he also felt that chronic empyema should not occur, or at least should become very rare, if this method is used in the treatment of the acute cases.

Gordon¹⁴² made a study of cases of chronic empyema at Camp Gordon which for the most part were originally caused by the hemolytic streptococcus, and found that these hemolytic streptococci played a minor part in those empyemata which developed into a chronic state. For long after these microorganisms were demonstrated to be absent from cultures from the wounds or from the secondary operative fluids, fetid purulent discharges continued to be given off, and closure of the wound was impossible. Furthermore, a high degree of immunity to the hemolytic streptococcus was demonstrated in these cases. On the other hand, a heterologous group of proteolytic bacilli, of which one group predominated, was observed in a large percentage of the cases. A variety of the proteus group was isolated from these secondary invaders, but the predominating organism among them in his series was a gram negative bacillus broadly belonging to the Friedländer group. The typical bacterial picture which he found in his cases of empyema accordingly showed the following sequence: (1) hemolytic streptococci in pure culture; (2) the gradual supplanting of the streptococci by a flora of secondary invaders, and (3) the freeing of the wound of these organisms under treatment, followed by closure.

Gordon further noted that the blood picture of chronic empyema, in contradistinction to acute cases in which the leukocytosis is high with a high percentage of polymorphonuclear cells, gives a low grade leukocytosis of about 10,000 cells per cubic centimeter, and a neutrophilia of from 60 to 70 per cent. A secondary anemia is invariably present in old and protracted cases.

141. Cauchoux, A.: A Discussion of the Causes and of the Evolution of the Treatment of Chronic Empyema, *Bull. méd., Par.* **34**:91 (Jan. 31) 1920.

142. Gordon, J. E.: The Bacteriology of Chronic Empyema, *J. Infect. Dis.* **26**:29 (Jan.) 1920.

Hirsh¹⁴³ reported a case of chronic empyema prolonged by osteomyelitis of several partially resected ribs, as being greatly benefitted by "diathermy," the peculiar current derived from a high frequency apparatus constructed just for this purpose. d'Heucqueville¹⁴⁴ showed by pneumographic tracings the advantage of deep respirations in helping to break up pleural adhesions. The after treatment for nonexpanded or partly expanded lung tissue, Goetze¹⁴⁵ claimed, is helped tremendously by the use of a mask so constructed that a valvelike adjustment, while permitting easy inspiration, makes expiration more difficult.

BRONCHIECTASIS, LUNG ABSCESS, AND PULMONARY GANGRENE

Elliott¹⁴⁶ reviewed forty cases of dilatation of the bronchi that he saw in one year, seven of them being in children. He noted that hemorrhage is frequent and may be slight or severe; also that clubbing of the fingers and toes is a very suggestive symptom, being noted as present in twenty-two of the forty cases, and possibly present in more. Nutrition was usually good and was of some assistance in differentiating from tuberculosis.

Menétrier and Durand¹⁴⁷ reported in detail a case of brain abscess which occurred apparently secondary to chronic bronchiectasis. At necropsy chains of streptococci were found in smears made from the brain abscess and from the bronchiectatic cavities.

In a discussion of the bronchoscopic treatment of bronchiectasis and lung abscess, Lynah¹⁴⁸ stated that although pulmonary drainage is difficult in all cases of circumscribed abscess, he believed the conservative bronchoscopic measures of treatment should be given a thorough trial first, before radical major surgery is attempted.

In another paper, Lynah¹⁴⁹ described his roentgenographic studies of bronchiectasis and lung abscess. He sterilized by boiling a 1:2 mixture of bismuth subcarbonate in pure olive oil, and slowly injected 8 c.c. of this mixture through a bronchoscope into the bronchi and

143. Hirsh, A. B.: Diathermy an Aid in Empyema, *Med. Rec.* **98**:1015 (Dec. 18) 1920.

144. d'Heucqueville, R.: Pneumography of Pleural Adhesions, *Presse méd.* **29**:164 (Feb. 26) 1921. *Abstr. J. A. M. A.* **76**:1136 (April 16) 1921.

145. Goetze, O.: Differential Pressure Mask for Empyema, *Zentralbl. f. Chir.* **47**:29 (Jan. 10) 1920.

146. Elliott, J. H.: Dilatation of the Bronchi: A Review of 40 Cases Observed June 1918—June 1919, *Med. Rec.* **98**:253 (Aug. 14) 1920.

147. Menétrier, P., and Durand A.: Brain Abscess at a Site Determined by Previous Trauma in a Case of Bronchiectasis: Development Suggesting Cerebrospinal Meningitis, *Bull. et mém. Soc. méd. d. hôp. de Par.* **44**:1066 (July 23) 1920.

148. Lynah, H. L.: Bronchoscopic Treatment of Bronchiectasis and Pulmonary Abscess, *Med. Rec.* **97**:215 (Feb. 7) 1920.

149. Lynah, H. L., and Stewart, W. H.: Roentgenographic Studies of Bronchiectasis and Lung Abscess after Direct Injection of Bismuth Mixture Through the Bronchoscope, *Am. J. Roentgenol.* **8**:49 (Feb.) 1921.

lungs of a living patient and apparently without danger. He considered the procedure of value in mapping out bronchiectatic and lung abscess cavities. In the first five cases, no harm was done the patients; in fact, the injections seemed to be of therapeutic benefit. The bismuth apparently is afterward got rid of gradually except where it has infiltrated the lung.

Clendening¹⁵⁰ noted that in the last few years lung abscesses after tonsillectomies have become more frequent than hitherto. He believed that there are four possible causes: (1) inspiration of infected material; (2) the use of motordriven anesthesia apparatus, creating a positive pressure in the pharynx; (3) metastatic infection through the lymphatics; (4) swabbing or tampering with the throat after enucleation has been accomplished.

Wessler and Schwarz¹⁵¹ described fifteen cases of lung abscess in infants and children, of which three followed the aspiration of a foreign body; five were subsequent to tonsillectomy, and seven were due to pneumonia or some other inflammatory condition. These authors emphasized the value of the roentgen ray not only for diagnosis but also for careful and exact oversight in the prognosis of these cases.

Foster¹⁵² told of a case of lung abscess, treated by artificial pneumothorax to collapse the lung, which came to necropsy six years later, after death from chronic nephritis. There had been a symptomatic cure of the lung abscess but peculiar physical signs had persisted, and "radiographs were useless, the involved area being covered by the heart shadow. At necropsy, the area of the abscess was found entirely replaced by dense fibrous tissue. The healing, in brief, had been perfect."

Netter¹⁵² reported the recovery of a boy from pulmonary gangrene under treatment with antigangrene serum made with the perfringens, the septic vibrio, and the malignant edema bacillus.

FOREIGN BODIES IN THE TRACHEA AND BRONCHI

Graham¹⁵³ wanted to enlist the interest of all pediatricians in the question of foreign bodies in the lungs or larger air passages, since 66 per cent. of foreign body cases are in children and many are undoubtedly overlooked. He stated that he suspects a foreign body in the lung if the following conditions are present: (1) localized lung

150. Clendening, L.: The Cause of Abscess of the Lung after Tonsillectomy, *J. A. M. A.* **74**:941 (April 3) 1920.

151. Wessler, H., and Schwarz, H.: Abscess of the Lungs in Infants and Children, *Am. J. Dis. Child.* **19**:137 (Feb.) 1920.

152. Netter: Pulmonary Gangrene, *Bull. et mém. Soc. méd. d. hôp. de Par.*, **45**:629 (May 6) 1921. *Abstr. J. A. M. A.* **76**:1862 (June 25) 1921.

153. Graham, E. E.: Foreign Bodies in the Air and Food Passages, *Am. J. Dis. Child.* **19**:119 (Feb.) 1920.

symptoms which persist in spite of treatment; (2) no tubercle bacilli in the sputum; (3) a leukocytosis for which there seems no definite reason, and (4) gradual failure in weight and health. The symptoms vary greatly; a peanut kernel almost immediately sets up a severe laryngitis, tracheitis, and bronchitis, known as arachidic bronchitis, while a metal object may remain in a long time and do comparatively little damage.

Jackson, Spencer and Manges,¹⁵⁴ discussed the diagnosis and localization of nonopaque foreign bodies in the bronchi, especially nut kernels, coffee berries, and maize beans, noting that while the roentgenogram usually failed to show such a foreign body itself, nevertheless it yielded three characteristic roentgenographic signs: (1) increased transparency over the entire affected side; (2) depression of the diaphragm on the affected side, and (3) displacement of the heart and mediastinal structures away from the affected side; in short, an acute obstructive emphysema. With the later development of abscess or of "drowned lung," distinct shadows of the pathologic condition may allow the definite localization of the nonopaque foreign body but then it may be too late. And, furthermore, the possibility of the shifting of the foreign body must always be kept in mind.

These same authors mentioned the following clinical features as helpful in localizing a foreign body: (1) the unobstructed side of the chest is fuller, harsh breathing is heard, and in the arachidic cases, is accompanied by very loud snoring snapping and bubbling râles; (2) the obstructed side has less expansion, has muffled tympanic resonance, and the breath sounds have a diminished intensity; (3) the intercostal spaces on the affected side may be retracted during inspiration. The signs, of course, may be considerably altered later. Dullness to flatness may intervene due to the accumulation of secretions in the air passages below the obstruction, a condition which has been termed "drowned lung."

The signs of foreign body which McCrae¹⁵⁵ considered of most value are the decreased expansion on the affected side, the presence of very fine râles, and the "asthmatoïd wheeze." Graham, and Jackson and his co-workers, also emphasized the value in the diagnosis of the presence of a foreign body, of this sign, the "asthmatoïd wheeze," which had been previously described by Jackson in 1918. McCrae wrote that it can be heard by placing the ear or the bell of the stethoscope close to the patient's mouth. It may be found with both inspira-

154. Jackson, C.; Spencer, W. H., and Manges, W. F.: The Diagnosis and Localization of Nonopaque Foreign Bodies in the Bronchi, *Am. J. Roentgenol.* **7**:277 (June) 1920.

155. McCrae, T.: The Physical Signs of Foreign Bodies in the Bronchi, *Am. J. M. Sc.* **159**:313 (March) 1920.

tion or expiration but sometimes is only audible at the end of forced expiration. It differs from the wheezing sounds heard with bronchial asthma but this difference is difficult to describe in words, he found. The sound varies in pitch and loudness depending on the character of the foreign body causing it. McCrae had never heard it over the chest wall.

Imperatori¹⁵⁶ reported six unusual cases of foreign bodies in the bronchi and commented on the frequency with which radiographs would have given the cause of obscure symptoms and prevented mistaken diagnosis.

RETROPHARYNGEAL ABSCESS

Friedman and Greenfield¹⁵⁷ believed that retropharyngeal abscess is of comparatively frequent occurrence though often overlooked. The disease consists of a suppurative lymphadenitis of the retropharyngeal glands situated on each side of the median line between the posterior pharyngeal wall and the aponeurosis covering the bodies of the cervical vertebrae. These glands drain the pharynx, postnasal spaces, Eustachian tubes and middle ears, and hence in infection of the various structures in these localities, they partake of the infection as do lymph glands in other parts of the body. Because of the usual atrophy and disappearance of the retropharyngeal glands at or about the fifth year, the process is rare except in young children. In the majority of their cases, the source was diseased tonsils and adenoids though frequently the disease can be attributed to a purulent rhinitis. They stated that the most pronounced clinical manifestations are those resulting from obstruction, the mechanical interference occasioned by the pressure of the mass in the pharynx. "When in the first year of life an infant ceases to suck well, chokes, coughs and is restless in sleep, we should always think of a retropharyngeal abscess." When a child has a rigid neck, or is suffering from hoarseness or from the various forms of croup, a careful examination of the pharynx is called for. The only possible way, these authors felt, of confirming or ruling out a diagnosis of retropharyngeal abscess is by palpation with the finger. They urged an early and adequate vertical incision in the faucial fluctuating mass with a bistoury, followed by finger exploration, and inversion of the child.

In a very recent article, Frank¹⁵⁸ has given an excellent exposition of the features of retropharyngeal abscess, discussing the anatomy,

156. Imperatori, C. J.: Foreign Bodies in Esophagus and Bronchi; 6 Cases, *New York M. J.* **113**:438 (March 16) 1921.

157. Friedman, J., and Greenfield, S. D.: Retropharyngeal Abscess; an Experience with 60 Cases, *New York M. J.* **113**:604 (April 20) 1921.

158. Frank, Ira: Retropharyngeal Abscess, *J. A. M. A.* **77**:517 (Aug. 13) 1921.

pathology, symptomatology, diagnosis, treatment, etc., of the disease. He brought out points similar to those mentioned above.

MISCELLANEOUS

Levy¹⁵⁹ collected from the literature twenty-one cases of congenital absence of one lung, and reported a twenty second case, with necropsy. Twelve of the cases died during the first year of life, but the other ten lived from ten to seventy years and then often came to necropsy for other than pulmonary conditions. Hence life is not incompatible with only one lung. There seemed to be a definite predilection for this anomaly for the left side, the ratio to the right side being two to one.

Cohen¹⁶⁰ classified the causes of cyanosis in the newborn as: (1) the character of the labor, the cyanosis being indicative of a real asphyxia, or due to intracranial hemorrhage. (2) Developmental causes, such as *a*, pulmonary atelectasis; *b*, congenital heart defects; *c*, thymus hyperplasia; and *d*, diaphragmatic hernia and other rare congenital anomalies. (3) Sepsis.

Faber¹⁶¹ noted the exceptional rarity of subcutaneous emphysema occurring spontaneously during the first days of life, and could find only two such cases reported in the literature, both being fatal cases reported by Guillot in 1853. Faber reported the case of an infant who developed a marked subcutaneous emphysema on the third day of life, following apparently a marked effort to breathe while lying on the face, with resulting alveolar rupture, perhaps due to a considerable negative or positive pressure on delicate lung tissue. The baby was treated by very careful and watchful nursing, the instructions being to avoid all crying if possible. The avoidance thereby of excessive increases in intrapulmonic pressure was sufficiently complete to allow air absorption to proceed at a greater rate than air escape, and so to permit the recovery which took place.

In a study of physical defects in two groups of children, Emerson¹⁶² noted that malnutrition, faulty teeth, postural defects, and mental backwardness were all apparently more common in children who suffered from nasopharyngeal defects than in those who had no such defects. However, in one of the groups of children studied, only 4 per cent. or presumably fourteen children were without nasopharyngeal defects so that percentages based on that number are hardly com-

159. Levy, C. S.: Congenital Absence of One Lung, *Am. J. M. Sc.* **159**: 237 (Feb.) 1920.

160. Cohen, F.: Cyanosis in the New Born, *Arch. Pediat.* **37**:666 (Nov.) 1920.

161. Faber, H. K.: Subcutaneous Emphysema in an Infant 3 Days Old, *Am. J. Dis. Child.* **19**:388 (May) 1920.

162. Emerson, W. R. P.: Physical Defects in Children, Report of 602 Cases, *Am. J. Dis. Child.* **21**:282 (March) 1921.

parable with percentages based on the other 96 per cent., or 343 children.

Fischer¹⁶³ reported the case of a 7 months old infant, who while playing with a box of dusting powder consisting chiefly of stearate of zinc, got a considerable quantity in his mouth. In twenty-four hours there were marked signs of respiratory obstruction, apparently in and around the larynx. Steam inhalations and emetics were without avail but stimulating expectorants, chiefly senega, proved successful and a recovery was made within three days.

Barnett¹⁶⁴ gave a short report of a 10 months old infant who poured half the contents of a jar of stearate of zinc down her throat. She immediately became cyanotic and limp and was stuporous at intervals. She developed a short hacking cough. The next day the temperature went up to 101 $\frac{3}{4}$ ° F. and diffuse fine râles were heard over both lungs, but four days later all signs had disappeared.

D'Oelsnitz and Carcopino¹⁶⁵ described the cases of two children, aged 2 and 3 years, respectively, with sudden development of suffocation presumably due to enlarged tracheobronchial glands affected by a wave of congestion or inflammation. Subsidence through the influence of the roentgen ray was almost as sudden as the onset.

In his discussion of the diagnosis and significance of tracheobronchial adenopathy, Balyeat¹⁶⁶ stated that he considered the d'Espine sign positive if a distinctly tracheal voice is heard below the seventh cervical vertebra in children less than 3 years of age, or below the first dorsal in children between 3 and 5, or below the third dorsal in children over 5. After analysing 449 cases, which were studied in whole or part by means of symptoms, signs and roentgen-ray findings, he drew a number of conclusions, among which were the following statements: A positive d'Espine is indicative of enlarged glands at the root of the lungs. This enlargement may be due to any one of several causes, the chief of which is an infection with the tubercle bacillus. When found in a poorly nourished child this sign usually is evidence of a tuberculous infection of the hilum. Chronic bronchitis will produce enlarged tracheobronchial glands which can be differentiated from a tuberculous hilum by means of the roentgen ray. If tonsillitis, whooping cough, or measles causes enlarged tracheobronchial glands,

163. Fischer, L.: Partial Asphyxiation in an Infant Resulting from the Inhalation of a Dusting Powder, *Med. Rec.* **98**:1027 (Dec. 18) 1920.

164. Barnett, N.: Insufflation of Stearate of Zinc, with Recovery, *Arch. Pediat.* **38**:53 (Jan.) 1921.

165. D'Oelsnitz and Carcopino: Tracheobronchial Adenopathies, *Bull. et mém. Soc. méd. d. hôp. de Par.* **45**:297 (March 4) 1921. *Abstr. J. A. M. A.* **76**:1281 (April 30) 1921.

166. Balyeat, R. M.: Diagnosis and Significance of Tracheobronchial Adenopathy, *J. A. M. A.* **76**:988 (April 9) 1921.

they are usually not of sufficient size or density to give a positive d'Espine.

Kernan¹⁶⁷ cited six cases in which bronchoscopy or esophagoscopy was instrumental in establishing the diagnosis of enlarged tracheo-bronchial glands, aneurysms of the aortic arch, neoplasms, etc. He advocated the more extensive employment of this diagnostic aid, especially in the hands of a skillful operator.

Imperatori¹⁶⁸ gave an outline of the symptoms due to lesions of the upper air passages and esophagus in which he believed endoscopy is of sufficient diagnostic value to warrant its habitual use. The opportunities for the use of the endoscope are apparently numerous.

Norris¹⁶⁹ believed that the roentgen ray can give information as to chest conditions with greater certainty than physical signs can, though it often does not do so. Proper team work and correlation of the facts are necessary. He urged that the radiologist be kept informed as to the clinical facts of the cases.

After an extensive review of the literature, Schlomovitz¹⁷⁰ concluded that pulmonary edema can be caused by the following factors: (1) The experimental production of pulmonary emboli. (2) Injury to pulmonary capillaries, either from within the vessels or from without. "The inflammatory type of pulmonary oedema which Sahli insisted on as the chief type in man, might be considered as a combination of intravascular and extravascular injury." (3) When the mechanical efficiency of the left ventricle is reduced to a greater extent than that of the right ventricle. (4) Combinations of causes.

Hoover¹⁷¹ discussed the various abnormalities of movement of the inner and outer portions of the costal margins during inspiration. He noted that these movements are modified with changes in the curve of the plane of the diaphragm caused by paresis of either the diaphragm or the intercostal muscles or by synechia between the diaphragm and the thoracic wall. He believed that such studies improve the accuracy with which one differentiates between infraphrenic and supraphrenic disease, and also enable both the estimation of the conformation of the heart and the size of the pericardial sack, and the differentiation between lesions which cause phrenic displacement and those which do not modify the plane of the diaphragm.

167. Kernan, J. D., Jr.: The Use of the Bronchoscope in the Diagnosis of Tumors of the Mediastinum, *New York State J. M.* **21**:115 (April) 1921.

168. Imperatori, C. J.: Endoscopy as a Diagnostic Aid in Diseases of the Upper Air Passages and Esophagus, *New York State J. M.* **21**:86 (March) 1921.

169. Norris, G. W.: Physical Diagnosis versus the X-ray in Disease of the Lungs, *New York M. J.* **112**:841 (Nov. 27) 1920.

170. Schlomovitz, B. H.: Experimental Pulmonary Edema, *Arch. Int. Med.* **25**:472 (April) 1920.

171. Hoover, C. F.: The Diagnostic Significance of Inspiratory Movements of the Costal Margins, *Am. J. M. Sc.* **159**:633 (May) 1920.

In a study of forced respiration and the experimental production of tetany, Grant and Goldman¹⁷² noted that forced respiration in the human subject causes symptoms of tetany to occur, including carpopedal spasm, Chvostek's sign, Trousseau's sign, Erb's sign, and in one instance a tetanic convulsion. As a result of the fall of alveolar carbon dioxid tension produced by overventilation, there is a reduction in the H ion concentration of the blood, a reduction of the carbon dioxid capacity of the plasma, a change in the reaction of the urine to the alkaline side, a decreased excretion of ammonia, and a slight increase in the calcium content of the serum. They believed that the underlying factor in the tetany of forced respiration is the alkalosis.

Gerstley¹⁷³ called attention to the necessity to consider not the disease alone nor even the disease and the patient alone, but the disease, and the patient, and the environment and living conditions. In illustration he cited the case of an 8 year old boy who because of a persistent dry hacking cough of some months' duration, had been to various physicians, had taken quantities of medicines, and even had been under the care of a Christian Science practitioner. There was nothing exceptional in the general history and physical and laboratory examinations. The chest itself was negative. The dry hacking nature of the cough suggested a nervous element. The father was somewhat neurotic. Further investigation disclosed that the parents were greatly worried about the condition and spoke constantly of the cough in the boy's presence. They had kept him indoors for some weeks, and, to cause him to relax, had given him a hot bath every night. To overcome the nervous element, parents and child were advised to forget the cough entirely. All medicine was stopped. The general measures to be taken were entirely those of building up the boy's resistance. In favorable weather he should go outdoors. He should have abundant rest and good food. Hot baths were to be replaced gradually by tepid, and later cool sponges. Within two weeks the boy was well.

In another case, Gerstley noted that a chronic cough was due to the child's mimicking of a nurse clearing her throat.

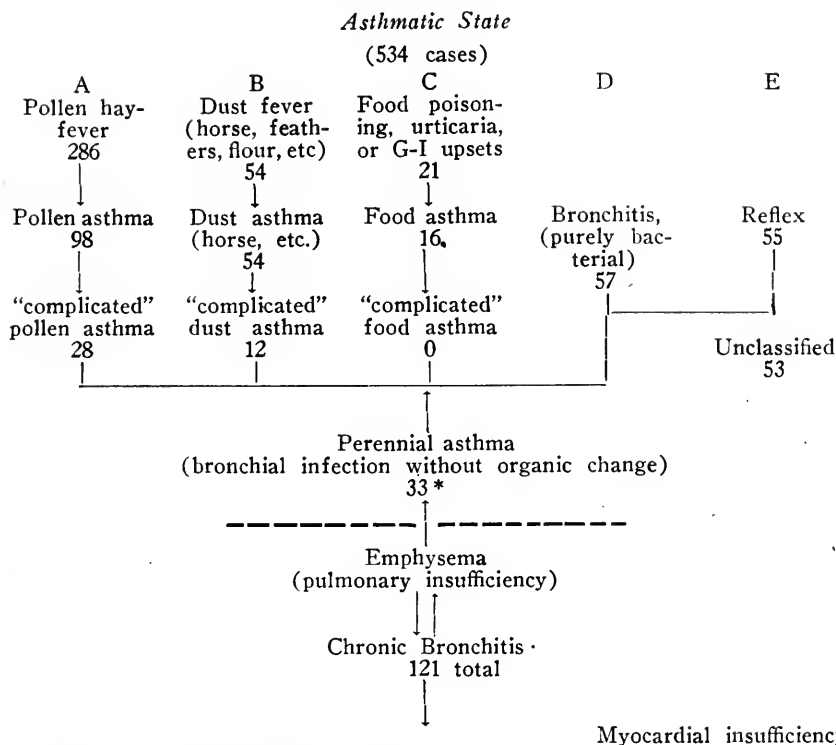
ASTHMA AND HAY-FEVER

Rackemann¹⁷⁴ noted the great variability of asthma and how it is frequently the result of a chronic bacterial infection of the bronchi superimposed on a long-standing foreign protein sensitization. He analyzed 534 cases in the following chart:

172. Grant, S. B., and Goldman, A.: A Study of Forced Respiration: Experimental Production of Tetany, *Am. J. Physiol.* **52**:209 (June) 1920.

173. Gerstley, J. R.: The New Era in Pediatrics, *J. A. M. A.* **76**:1633 (June 11) 1921.

174. Rackemann, F. M.: The Vaccine Treatment of Asthma, *M. Clinics N. America* **4**:1751 (May) 1921.



* New cases originating in this group.

For a classification of asthma as it occurs in infancy and children, Schloss,¹⁷⁵ in his classical description of allergy in infants and children, noted two of the clinical types of allergy in which asthma is a feature. The first is the hyperacute type with urticaria, asthma, and symptoms of shock. This is most commonly due to milk or egg, occasionally to beef. It is also observed in susceptible individuals after the injection of horse serum. All the symptoms usually appear within a few minutes, as after the injection of a particular food. Usually very little of the food is actually ingested as the infant spits it out of his mouth or vomits immediately after it has been swallowed. Within a few minutes there is a swelling of the lips, tongue, and buccal mucous membrane. Symptoms of collapse occur, and the patient becomes drowsy or somnolent; shortly afterward, there is marked general urticaria. Asthma commonly occurs immediately after the food is swallowed and is usually severe. It occurs in many cases but not in all. It may be absent in the earlier attacks, but present in later ones. Sneezing and conjunctival congestion are usually pronounced. The severe symptoms

175. Schloss, O. M.: Allergy in Infants and Children, *Am. J. Dis. Child.* 19:433 (June) 1920.

usually subside within an hour or two, the urticaria may last from sixteen to twenty-four hours.

The second type according to Schloss is bronchial asthma, which may be due to the proteins of food, pollens, epidermis of animals, and bacteria.

In a study of sensitization in bronchial asthma, Caulfield¹⁷⁶ developed two general impressions: (1) Bronchial asthma is a syndrome with quite wide variations. It frequently requires a very broad type of investigation if all the possible etiological factors which may be operative in the individual case are to be considered, and (2) despite the fullest type of investigation there will remain a percentage of cases which one must regard as typical examples of true bronchial asthma but for which no definite etiology can be demonstrated. Between these cases and those in which protein sensitization has been clearly established, there may be no detectable difference except that they are protein negative. (to between seventy and eighty proteins). He thought that among some of the patients presenting the syndrome of bronchial asthma, and as well in a very large majority of hay-fever patients, there is evidence that the lesion is an immunologic one, closely analogous to, if not identical with, the experimentally produced phenomenon called anaphylaxis.

Coke¹⁷⁷ believed that half the cases of asthma can be proved by skin reactions to be due to some foreign protein. He wrote that asthma, hay-fever, urticaria, eczema, migraine, epilepsy and paroxysmal hemoglobinuria, have many common traits, and will probably all be proved eventually to be symptoms of anaphylaxis and not separate diseases at all.

Rackemann,¹⁷⁸ on the other hand, suggested that hay-fever may depend on a mechanism which is not anaphylactic but which is perhaps closely associated with that of drug idiosyncrasies.

From his personal observations on 150 cases of bronchial asthma, Piness¹⁷⁹ concluded that heredity is an important predisposing but not exciting factor in from 25 to 50 per cent. of the cases. By means of cutaneous tests he found it possible to determine the etiology in from 47 to 50 per cent. of the cases, and multiple sensitization was common, especially in the food and pollen groups. Sensitization to one protein in early life seemed apt to be followed by sensitization to other proteins

176. Caulfield, A. H. W.: Sensitization in Bronchial Asthma and Hay-Fever, *J. A. M. A.* **76**:1071 (April 16) 1921.

177. Coke, F.: Asthma and Anaphylaxis, *Brit. M. J.* **1**:372 (March 12) 1921. *Abstr. J. A. M. A.* **76**:1045 (April 9) 1921.

178. Rackemann, F. M.: *The Specific Treatment of Hay-Fever*, Boston M. & S. J. **182**:295 (March) 1920.

179. Piness, G.: Etiology of 150 Cases of Bronchial Asthma, *California State J. Med.* **19**:29 (Jan.) 1921.

but patients with a history of onset past thirty-five years of age rarely give positive skin reactions, he noted. His final conclusion was that endocrine dysfunction bears a prominent part in the etiology of asthma, particularly in the young individuals, and should be borne in mind where the patient does not respond to specific protein therapy.

In a clinical discussion of the diagnosis and treatment of asthma, hay-fever, and allied conditions, Rackemann¹⁸⁰ called particular attention to the importance of a careful history and a complete physical examination.

Alexander and Paddock,¹⁸¹ in their study of the response to pilocarpin and epinephrin of patients with bronchial asthma, found that in a series of such cases a general examination with routine laboratory aids and drug tests revealed no constant associated condition, but the most frequent finding was abnormally increased sensitiveness to pilocarpin. The majority of cases reacted also to epinephrin with an abnormal rise in blood pressure and other characteristic signs—pallor, tremor, sometimes rigor, denoting increased sensitiveness to this drug. A relation between low blood pressure and this excessive epinephrin reaction was apparent, while the smaller number of cases with normal or high blood pressure gave regularly normal reactions. The former cases, those reacting excessively to epinephrin, were found to be relieved by 0.25 c.c., a much smaller dose of the drug than is usually employed.

Both Shambaugh¹⁸² and Jesberg¹⁸³ called attention to the fact that asthma is often associated with definite pathologic changes in the nasal cavity. Shambaugh stated that the pathologic condition associated with most cases of asthma was a hyperplastic ethmoiditis, and he found that a correction of this condition had a very decided influence on the asthma. The relation between the nasal condition and asthma appeared to be not so much one of a nasal reflex neurosis as an anaphylactic reaction, but he felt that the improvement in the asthma resulting from operations in the ethmoid may be due to the elimination of foci harboring bacteria and their toxins.

Jesberg¹⁸³ thought that the nasal disorders were usually a hyperplasia leading to further disease of the accessory sinuses. He attributed the hyperesthesia of the nasal mucosa, in part, to the primary condition causing the asthma and, in part, to the subsequent pathology in the

180. Rackemann, F. M.: Asthma, Hay-Fever, and Allied Conditions, *M. Clinics N. America* **3**:1065 (Jan.) 1920.

181. Alexander, H. L., and Paddock, R.: Bronchial Asthma; Response to Pilocarpin and Epinephrin, *Arch. Int. Med.* **27**:184 (Feb. 15) 1921.

182. Shambaugh, G. E.: The Nasal Cavities and Asthma, *Illinois M. J.* **39**: 10 (Jan.) 1921.

183. Jesberg, S.: A Study of Nasal Conditions Occurring in Bronchial Asthma, *California State J. M.* **19**:33 (Jan.) 1921.

nose. This nasal pathology tends to maintain the asthma even after the primary cause has been disposed of, and accordingly he felt that the rhinologist should work in coöperation with the internist, eliminating the nasal factor of the disease in the interest of permanent cure of these sufferers.

In advocating the early removal of enlarged adenoids in infants, Freeman¹⁸⁴ stated that adenoid obstruction in infancy leads to a number of reflex manifestations which are not usually recognized as having any relation to adenoid obstruction. Among these he included failure to gain in weight, restlessness, convulsions, eczema and asthma.

Rackemann¹⁸⁵ stated that in treating asthma, one must recognize that it is a symptom complex which depends on one or the other of two great groups of causes. Either the cause is a foreign protein which exerts its influence from outside the body, i. e., an extrinsic cause, or it produces its effects from some focus usually of bacterial growth and action within the body, an intrinsic cause. The treatment of this last group consists either in eradicating the focus by surgical means, if possible, or in the use of bacterial vaccines made preferably from the same strains which are causing the focus of infection, or finally by surgery and vaccination together. Inasmuch as the search for a focus is usually futile, it is assumed that a chronic infection of the bronchi is responsible for the asthma and vaccines are prepared from the sputum bacteria.

In discussing this vaccine treatment of intrinsic asthma, Rackemann believed that the following line of argument is permissible, granting that the results of the treatment are substantial and that the importance of a positive skin test as a prerequisite to successful treatment is not overestimated. It is known that in horse asthma and ragweed pollen asthma, the symptoms depend on an exquisite sensitiveness to the particular foreign protein. Inasmuch as circulating antibodies are not formed we assume that this condition of sensitiveness is cellular. The specific protein will produce a positive skin test and repeated injections will cause relief of symptoms. This treatment is specific. In intrinsic asthma, vaccines likewise produce a positive skin test and as treatment with them is successful only in case the test is positive, their action is specific. By analogy, therefore, we may assume that asthma due to bacteria depends probably on a condition of specific cellular sensitiveness either to the bacteria themselves or to the product of their action in the organism.

184. Freeman, R. G.: The Results of the Presence of Adenoids in Infancy, *New York State J. M.* **21**:50 (Feb.) 1921.

185. Rackemann, F. M.: The Relation of Sputum Bacteria to Asthma, *J. Immunol.* **5**:373 (July) 1920.

In his summary, D. W. C. Jones¹⁸⁶ stated that in the treatment of asthma, one has to consider an irritable center, the hysterical influence of that center, infections of the bronchi and parts of the lungs below them, more especially with specific bacteria whose toxins induce the paroxysms, abnormalities of the respiratory tract superior to the bronchi, and irritation of viscera outside the respiratory tract altogether.

Caulfield¹⁷⁶ gave in detail his technic for the intracutaneous tests, and stated that he felt that at present we have no satisfactory evidence that the injudicious use of a polyvalent solution may not sensitize a patient against other pollens than those to which he was originally sensitive. Gottlieb¹⁸⁷ described the technic of specific therapy, and Mackenzie¹⁸⁸ described the method of desensitization necessary when it is desired to give diphtheria or other antitoxin or pneumococcus Type I serum to "horse" asthmatics or victims of an allergic rhinitis.

Hutcheson and Budd¹⁸⁹ treated eighty-one cases of bronchial asthma with vaccines. About 75 per cent. showed definite improvement, and of those who were considered unimproved, none had had a second series of injections.

As for the drug treatment of asthma, Marfan¹⁹⁰ noted that small doses of potassium iodid, kept up for months or years, had proved useful to ward off the tendency, but for the attacks themselves subcutaneous injections of epinephrin once or twice a day had been effectual. But epinephrin loses its relieving effects on asthma patients after repeated doses, according to Gottlieb,¹⁸⁷ and probably also is not without deleterious effects through its constant elevation of the blood pressure. Gottlieb also described the preventive, climatic and drug treatment of asthma, and noted the surprising relief obtained by inhaling the fumes from a smouldering powder made from nine parts of stramonium leaves and one part of potassium nitrate. In two boys in whom pulmonary emphysema was considered responsible for the attacks of asthma, LeClerc¹⁹¹ used tartar emetic first and then injections of from 2 to 4 cg. of emetin daily for five days and another series of injections after an interval of from five to ten days. There was a gradual disappearance of the symptoms, and four years later

186. Jones, D. W. C.: The Factors Concerned in Asthma, and Their Treatment, *Lancet* **1**:484 (Feb. 28) 1920.

187. Gottlieb, M. J.: The Treatment of Bronchial Asthma, *J. A. M. A.* **74**: 931 (April 3) 1920.

188. Mackenzie, G. M.: Serum Desensitization, *J. A. M. A.* **76**:1563 (June 4) 1921.

189. Hutcheson, J. M., and Budd, S. W.: The Treatment of Bronchial Asthma with Vaccines, *Virginia M. Monthly* **46**:281 (Feb.) 1920.

190. Marfan, A. B.: Asthma in Infants, *Presse méd.* **28**:481 (July 17) 1920.

191. LeClerc, R.: Emphysema of Asthmatic Type, and Emetine Chlorhydrate, *Bull. et mém. Soc. méd. d. hôp. de Par.* **44**:802 (June 11) 1920.

one of the boys was found to be still free from the symptoms and signs of asthma.

Hay-Fever.—Walker¹⁹² whose writings on this subject are among the most authoritative today, discussed in detail the various causes of seasonal hay-fever, and the methods of determining these causes and the degree of sensitization. He also described the methods of immunization.

Rackemann¹⁷⁸ described his method of treatment for ragweed hay-fever and noted that in ninety-one patients, eight were entirely freed of their symptoms and fifty-seven were considerably relieved. Of the remaining twenty-six patients, fourteen showed some slight relief while twelve had absolutely no relief or were even worse.

In a discussion of "group reactions" in hay-fever, Caulfield¹⁷⁶ stated that from the entire absence of correlation between different pollens to which different patients have been shown to be sensitive, the evidence at present available points strongly against group reaction and suggests on the contrary that sensitization for one pollen is entirely specific for that pollen only. But after a successful desensitization with one pollen, any subsequent desensitization against a different pollen was more easily and rapidly accomplished.

192. Walker, I. C.: The Causes and Treatment of Seasonal Hay-Fever, *M. Clinics N. America* 4:1673 (May) 1921.

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NEPHRITIS IN CHILDREN *

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These investigations were carried out to determine the functional pathology of the nephritides in children. Little data was found in the literature when this work was begun. Since that time Hill¹ has reported on some fairly extensive work along this line. The preponderance of acute over chronic cases in childhood affords an opportunity for the study of the disease at its inception which is unique in civilian practice. All cases of nephritis admitted to the wards were placed in my charge and in this way close cooperation between the ward and the laboratory was maintained.

ETIOLOGY

Infections, often apparently insignificant, were the most important etiologic factors in a series of twenty-six cases.

TABLE 1.—SOURCE OF INFECTION IN TWENTY-SIX CASES OF NEPHRITIS

Disease	Number of Cases	Per Cent.
Tonsillitis.....	11	42.3
Scarlet fever.....	4	15.4
Otitis media.....	3	11.6
Nasopharyngitis.....	3	11.6
Umbilical infection.....	1	3.9
Mercuric chlorid.....	1	3.9
Unknown.....	3	11.6

The tonsillitis was only revealed by the examination of the tonsils in some cases, no complaint of sore throat having been made. Cultures from the tonsils in two of these cases gave pure cultures of *Streptococcus hemolyticus*.

Blood cultures were made in five cases, in three of which *Streptococcus hemolyticus* was found. Urinary cultures proved of little value, only two out of eleven showing any growth, and in those two cases there was an associated pyelitis.

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* From the wards and Pathological and Chemical Research Laboratories, Hospital for Sick Children, and the Department of Pediatrics, University of Toronto.

1. Hill, L. W.: Am. J. Dis. Child. **14**:267 (Oct.) 1917.

A moderate leukocytosis was present in uncomplicated cases. This increase was lymphocytic in character, from 50 to 60 per cent. of the white cells being lymphocytes. A more marked secondary anemia than could be accounted for by the hematuria was present in most cases. The color index was less than one in cases with hemoglobin of 50 per cent. or less, as the number of red blood corpuscles was not reduced to the same extent as the hemoglobin.

An elevation of blood pressure was absent or of moderate degree in most cases. A rise of 120 mm., if maintained, indicated a bad prognosis. These findings agree with those of Berkeley and Lee.² The systolic pressure rose to 180, or more, in only two cases of fatal uremia. No relationship between urinary or blood findings and the rise of blood pressure was demonstrable.

The observations of Baginsky,³ and of Hill⁴ on the rarity of cardiac hypertrophy in children with nephritis were borne out in our series. Enlargement of the heart, except as a terminal dilatation, was not seen in any case. The liver was enlarged in 50 per cent. of the cases. The spleen was palpable in six cases.

Eye-ground changes are infrequent. Retinal hemorrhages were seen in two fatal cases. Pallor of the optic discs was present in three cases as a part of the general condition. Venous distension around the optic disc was seen in one case. In no instance were the typical retinal changes associated with nephritis seen.

PLAN OF INVESTIGATION

Daily examinations of the urine were made to determine its quantity, specific gravity, presence or absence of macroscopic blood, the amount of albumin (Esbach's method) and the chlorid excretion by the method of Volhard.⁵ Frequent microscopic examinations of sediment from fresh specimens was made to study the pathologic constituents.

Chemical examinations of the blood were made from time to time during the patient's stay in hospital. The nonprotein nitrogen, creatinin, and sugar were determined by the micromethod of Folin and Wu,⁶ the urea nitrogen by Van Slyke and Cullen's method,⁷ and the chlorids were estimated by Rappelye's⁸ modification of Volhard's method.

2. Berkeley, H. K., and Lee, J. W.: *Am. J. Dis. Child.* **13**:354 (April) 1917.

3. Baginsky: *Arch. f. Kinderh.* 1902.

4. Hill, L. W.: *Am. J. Dis. Child.* **17**:270 (April) 1919; *M. Clinics N. America* **2**:1419 (March) 1919; *J. A. M. A.* **73**:1650 (June) 1919.

5. Volhard and Harney: *Arch. Int. Med.* **6**:12, 1910.

6. Folin and Wu: *J. Biol. Chem.* **38**:81, 1919.

7. Van Slyke and Cullen: *J. A. M. A.* **62**:1558 (May 16) 1914.

8. Rappelye: *J. Biol. Chem.* **32**:509, 1918.

The kidney's ability to concentrate was studied by placing the patient on a dry diet (less than 10 ounces fluid in twenty-four hours) from 6 o'clock the night before the test until its completion, collecting two hour specimens of urine during the day and a twelve hour specimen at night, and determining the quantity and specific gravity of these specimens. In normal children the specific gravity varied at least ten points during the day. The specific gravity of the night urine was usually 1.035.

The diluting and water excreting powers of the kidney were determined by giving a large quantity of water by mouth within a short time, and after emptying the bladder specimens were collected at short intervals. The amount of urine passed in the twenty-four hours, its lowest specific gravity and rate of excretion furnished the desired information. The normal child excreted between 80 and 90 per cent. of the total within four hours, and the whole amount, or more, in twenty-four hours. The specific gravity was as low as 1.001 in some specimens. In the charts, failure to excrete 80 per cent. in the first four hours but excretion of the ingested amount in the twenty-four hours is marked "delayed;" failure to do either is designated "poor." The lowest specific gravity is indicated.

The elimination of the kidney's normal excretory products was estimated by the daily chlorid excretion on a salt free diet and the response to the ingestion of 5 gm. sodium chlorid. The actual amount excreted and its effect on urinary flow were noted.

The phenolsulphonephthalein test was done after the technic of Rowntree and Geraghty,⁹ with the exception that when much edema was present the drug was given intravenously, at other times intramuscularly. The normal response to this test in children is the excretion of from 60 to 75 per cent. of the drug in two hours.

CLASSIFICATION OF CASES

Our series was divided into three main groups of cases: (1) the acute, comprising twenty-four cases; (2) chronic glomerulonephritis, two cases, and (3) nephrosis, one case. The acute cases were further subdivided into those in which progress toward recovery was rapid and steady, and those which tended to become chronic, i.e., into resolving and nonresolving groups. Those cases which terminated fatally are treated in a section by themselves.

1. *Acute Resolving Nephritis*.—Fifty per cent. of the acute nephritides fell into this group. Admission to the hospital usually occurred during the first week of the disease; some cases, however, were further advanced. The usual history was that of an acute upper

9. Rowntree and Geraghty: J. A. M. A. 67:811, 816 (Sept. 2) 1911.

TABLE 1.—ACUTE CASES; RECOVERY . . .

Name, Age, Date of Admission	Day of Discharge	Temperature	Edema	Eye-grounds	Urine			Blood Pressure		Concentration Test	Water Test	Phenol-sulphophthal-ein	Added NaCl	Blood				Chlor-ids			
					Amount	Specific Gravity	Albu-min	Chlor-ids	Mac. Blood					Sys-tolic	Diast-olic	Urea N	Uric Acid		Creat-inin	Sugar	
1. W. L. 5 yrs. 10/22/19	32	100	++	N	750	1.012	0.2	++	125	90	1017-1038	46.2	25.5	1.9	3.7	0.14	0.63	
	33	98.9	++	..	268	1.020	+++	
	36	98	++	..	456	1.012	+++	Delayed 1005	
	38	..	++	
	40	..	++	..	594	1.020	0.08	3.05	++	
	46	98	++	..	940	1.018	0.08	1.03	++	
	52	98	++	..	700	1.020	0.08	1.36	++	105	85	
	78	98.4	++	..	700	1.028	0.01	2.8	+	
	79	98	0	..	1,000	1.018	0	2.0	0	
	90	98	0	N	800	1.023	0	4.3	0	
2. P. C. 4 yrs. 11/13/19	82	98	0	..	900	1.022	0	3.1	0	1016-1030	
	84	824	1.026	0	2.8	0	Good	
	85	..	0	..	940	1.023	0	7.0	0	
	98.4	..	+	N	194	1.030	0	105	80	1025-1030	30.1	25.0	2.2	2.9	0.09	0.56	
	98.6	..	+	0	
	43	..	+	..	400	1.017	0.09	0.84	0	
	57	..	0	..	500	1.020	0.08	0.84	0	
	67	98	0	..	600	1.030	0.30	2.97	0	
	85	..	0	..	500	1.030	0.13	7.80	0	
	87	..	0	..	764	1.028	0.15	4.2	0	
3. F. R. 5 yrs. 11/11/19	90	..	0	..	600	1.027	0	3.8	0	
	110	..	0	N	630	1.028	0	3.6	0	1017-54	
	98	..	+	N	246	1.020	0.5	0	105	84	1020	
	26	474	1.015	0.4	1.09	0	
	27	800	1.020	0.02	4.64	0	
	41	
	42	474	1.020	0	3.6	0	
	50	1,010	1.010	0	2.2	0	
	13	99	+	N	480	1.028	0.5	+	110	90	
	8 yrs. 12/5/19	19	98	..	872	1.020	0.5	+++	
4. A. M. 8 yrs. 10/20/19	21	390	1.025	0	3.77	0	1018-1028	
	99	..	+	N	116	85	
	3*	98	+	
	4	98	+	
	98	..	+	..	390	1.032	0.25	3.12	0	102	80	
	111	98.6	0	..	240	1.041	0.20	2.13	0	Good 1002	
	115	98	0	..	468	1.030	0	4.07	0	
	120	98	0	
	124	98	0	..	240	1.037	0	1.46	0	1013-1037	
	5. R. C. 8 yrs. 10/20/19	99	..	+	N	116	85
3*		98	+	
4		98	+	
98		..	+	
98.6		..	0	
115		98	0	
120		98	0	
124		98	0	
6. F. R. 5 yrs. 11/11/19		23	98	+	N	246	1.020	0.5	0	105	84	1020
		26	474	1.015	0.4	1.09	0
	27	800	1.020	0.02	4.64	0	
	41	
	42	474	1.020	0	3.6	0	
	50	1,010	1.010	0	2.2	0	
	13	99	+	N	480	1.028	0.5	+	110	90	
	8 yrs. 12/5/19	19	98	..	872	1.020	0.5	+++	
	21	390	1.025	0	3.77	0	
	7. R. C. 8 yrs. 10/20/19	99	..	+	N	116	85
3*		98	+	
4		98	+	
98		..	+	
98.6		..	0	
111		98	0	
115		98	0	
120		98	0	
124		98	0	

6. B. S. 5 yrs. 5/26/21	5 20 24	98.6	+	..	300 500 650	1.022 1.025 1.022	1.0 0 0	0.06 1.00 1.40	+++ 0 0	100	85	1020-1030	Good 1004 ..	60.0 65.0	31.8	25.0	8.3	3.82	0.100	0.77
7. R. H. 11 yrs. 3/5/20	3 21 24 26 30	104 98.6 .. 98 98	+	..	600 420 383 600 825	1.020 1.030 1.025 1.022 1.022	3.0 0.15 0.40 0.02 0	.. 1.80 1.47 6.12 3.18	+++ 0 0 0 0	118 100 ..	90 85 ..	1021-1030	Good 1004 ..	59.8	Good ..	84.02 51.9	72.0 ..	10.0 3.3	4.02 2.17	0.092 0.09	0.40 0.572
8. N. M. 9 yrs. 11/11/20	7 20 22 24 26	98 98.6 98	+	N	690 620 570 1350 900	1.018 1.018 1.027 1.012 1.015	0.30 0 0 0 0	0.384 0.400 0.378 1.04 3.08	0 0 0 0 0	100	80	1016-1030	Good 1005 ..	43.3	Good ..	27.2	18.9	1.8	1.4
9. J. C. 11½ mos. 11/3/20	39 36 40	99 .. 98	+	N	390 460 475	1.014 1.012 1.013	0.40 0.30 0	1.88 0.876 1.20	++ 0 0	63.3 .. 65.0	..	42.2	35.0	5.5	1.4	0.110	0.095
10. S. L. 12½ mos. 2/10/21	24 14 24 25 34 50 58	104 .. 98 .. 98 98 98	+	..	250 560 570 386 1020 660 700	1.017 1.014 1.020 1.020 1.015 1.019 1.020	3.75 2.00 3.0 3.0 1.3 1.0 0	0.675 0.210 .. 0.855 1.710 6.41 3.10	+++ + 0 0 0 0 0	110	80 1010-1020	Good 1005 50.0	..	102.0	92.0	2.5	2.0	0.106	..
11. M. R. 2 wks. 12/30/20	7 10	98.8 ..	0	1.007 1.006	1.0 0.5	0.85 0.78	0 0	39.1	31.4	3.2	1.6	0.083	0.58
12. J. B. 8 yrs. 11/26/20	5 6 28 33 36 40 51 80 81 95 96 120	99 98.6 .. 98 98 98 98 98	++	N	770 640 800 1675 700 810 1210 250 390 545 1200	1.023 1.018 1.020 1.070 1.010 1.020 1.017 1.018 1.021 1.023 1.021	+++ 1.3 1.25 1.50 0.20 0.2 2.0 0.6 1.5 2.0 0	.. 3.92 1.424 5.69 1.62 1.63 1.68 2.65 0.675 2.19 1.8	0 ++ ++ ++ 0 0 0 +++ 0 0 0	100	80	1012-1023	Good 1004	44.7	38.0	4.1	3.3	0.091	..
												1020-1025	50.0	..	32.3	18.9	..	2.9

* K. L.

† Scarlet fever, erysipelas.

‡ K. L. (51).

§ Varicella (81).

respiratory tract or tonsil infection, followed in a day or so by more or less complete suppression of urine, which was succeeded by hematuria. Slight edema of the lower eyelids and about the ankles was common, but in only two cases was there general anasarca. The edema usually disappeared within ten days, unaccompanied by marked diuresis, but with a persistently increased excretion. Ophthalmoscopic examination was made in each case but nothing abnormal was seen. Only two cases, (Cases 1 and 7, Table 1), showed any increase in blood pressure, and in both cases it fell to normal when the edema disappeared. The only elevation of temperature (Case 10) occurring was due to the initial infection and fell to normal when it subsided. The hematuria usually persisted from two to four weeks, and showed a tendency to recur following tonsillectomy or the administration of an irritant, e.g., sodium chlorid. The average stay in hospital was two months, varying from two weeks to four months in individual cases. The patient was not discharged until all evidence of kidney inflammation had subsided. Five (Cases 3, 4, 5, 10 and 11), of these children have been seen at the nephritic clinic since their discharge. Four show no evidence of nephritis in either the blood or urine and are apparently in good condition physically.

Functional Studies.—The initial low excretion of urine was replaced by a normal output within two weeks. Albumin, to the extent of 1 or 2 gm. per liter, was present during the first week or two, after which it fell to a trace which usually persisted long after other evidences of trouble had disappeared. The excretion of chlorid on a salt free diet was good, and additional salt in the diet, when the acute symptoms had subsided, was promptly eliminated by an increased concentration of the urine. The administration of the sodium chlorid in two of the cases resulted in a reappearance of the hematuria. Microscopically, the urine contained blood cells and large mononuclear cells. Casts were only evident at first when the numerous red blood cells were laked, causing the appearance of an apparent increase in casts as the hematuria cleared up. The casts were chiefly finely granular and hyalin, few blood casts being seen, even when the urine contained much blood.

The phenolsulphonephthalein test proved of little value until all acute symptoms had subsided, being as low as 22 (Case 3) and as high as 60 (Case 2) in cases otherwise comparable. When the disease became quiescent, the phenolsulphonephthalein excretion usually rose to normal. Transitory hematuria followed the giving of the drug in two cases.

Impairment of the kidney's ability to concentrate was noted in only one case of this group at the time of discharge. Some fixation at a

TABLE 2.—ACUTE CASES OF NEPHRITIS BECOMING CHRONIC

Name, Age, Date of Admis- sion	Day of Dis- ease	Tem- pera- ture	Edema	Eye- grounds	Urine				Blood Pressure		Con- centra- tion Test	Water Test	Phenol- sul- phone- phthal- ein	Added NaCl	Blood				
					Amount	Specific Gravity	Albu- min	Chlor- ids	Mac. Blood	Sys- tolic					Diast- olic	Urea N	Uric Acid	Creat- inin	Sugar
1. N. M. 5 yrs. 10/9/19	14	98.8	++	N	520	1.024	2.8	0.052	0	102	70	19.4	23.5	1.8	1.5	0.108	0.60
	24	98.6	++	..	243	1.030	115	80
	27	98	+	..	660	1.026	Delayed 1002
	61	98	0	N	600	1.024	1.0	2.28	0	70.0	Poor	18.4	...	1.6
	63	98	0	..	640	1.021	0.8	4.48	0
2. O. L. 12 yrs. 11/30/20 1/3/21	67	415	1.028	1.5	2.19	0
	89	98	0	N	460	1.032	0.25	3.53	0
	100	100	++	N	200	1.015	1.00	++	100	80
	14	98	++	++
	18	98	++	..	250	1.014	0.80	2.13	0
3. J. P. 10 yrs. 11/24/19	412	98.8	+	N	450	1.023	1.0	+
	7	99.8	++	140	95
	15	99	+	++	122	78
	17	99	+	..	600	1.020	1.5	++
	24	98	840	1.015	1.0	2.57	+	Good 1020
4. E. B. 14 yrs. 3/3/21	25	98	0	..	570	1.020	0.5	4.85	+
	26	98	0	..	540	1.020	0.5	2.16	+
	70	98.6	0	N	760	1.015	2.2	1.748	++	110	65
	74	..	0	..	650	1.014	1.5	0.682	++
	76	..	0	..	472	1.013	2.0	0.531	++	Delayed 1004
5. M. C. 13 yrs. 12/7/20	82	98	0	..	1150	1.012	3.8	+
	86*	98.6	0	..	900	1.012	0.2	1.59	0
	96	99.8	0	..	870	1.016	3.2	0.48	++
	98	98	0	..	840	1.013	0.2	0
	100	99.4	+++	..	600	1.013	4.5	+++
6. E. S. 7 yrs. 2/11/21	27	100	+++	..	825	1.015	2.0	0.08	++	145	118
	31	98	+	..	569	1.016	1.2	1.47	++
	34	101	+	..	840	1.015	0.8	5.75	++
	49	102	+	..	800	1.015	0.5	+
	58	98	0	..	1,000	1.010	0.3	1.77	0	Delayed 1020-1021-1005
6. E. S. 7 yrs. 2/11/21	60	..	0	..	500	1.021	0.4	1.80	0
	42	99	0	..	980	1.015	1.0	0.98	++
	46	99.2	0	..	420	1.018	1.8	0.96	++	110	80
	55	100	0	..	635	1.010	0.5	0.80	0
	57	98.6	0	..	700	1.013	2.0	1.95	0
58	98	0	..	750	1.013	1.5	0.80	0	

* K. L.

high level was observed during the acute stage in two cases (Cases 1 and 8).

Early in the disease the ingestion of a large amount of water was not usually followed immediately by any marked diuresis, but even at that time the entire amount was excreted in the first twenty-four hours. After recovery from the acute symptoms, water excretion was normal. In only one case (Case 8) of this group was the water retained with resulting increase in the edema. In this case the kidney's ability to excrete water remained impaired.

Only slight increase in the nonprotein nitrogen constituents of the blood at any stage of the disease was seen in these cases. The only exception to this was in a child (Case 10) with lobar pneumonia, when it was as high as 84 mg. per hundred c.c., but coincidentally with the fall in temperature it became normal. A relative increase in the urea nitrogen to 65 or 75 per cent. of the total nonprotein nitrogen, in place of the usual 50 per cent., was common. The creatinin never rose above 3 mg. per hundred c.c., and in most instances remained below two. No deviation from the normal blood sugar content was observed. The plasma chlorids were normal in all but one case (Case 6) with a slight but persistent edema.

2. *Acute Nonresolving Nephritis*.—Six cases (Table 2) presented evidence of being a more severe type of the disease than those of the last group. Admission to the hospital varied from one to ten weeks, usually two, after the onset of the disease. The severity of the acute symptoms had not abated at this time. Fever, without apparent exciting cause, was common. The hematuria tended to be periodic, and was generally present, at times for two months or longer. Well marked edema or anasarca of a persistent type was usual. The edema lasted five or six weeks, and later was easily produced by a slight infection or by dietetic errors. A rise in blood pressure, slight but maintained over weeks, was noted in all but one case (Case 2). Congestion of the retinal vessels was the only pathologic change found in the eyegrounds, and this occurred in only two cases (Cases 5 and 6). Severe secondary anemia was present in all cases. Only one patient (Case 5) of this group is attending the outdoor clinic now, one year after the acute attack. She is below par physically and still has albuminuria and cylindruria.

The functional studies furnished earlier indications of the severity of these cases than was obtainable by clinical observations. The reestablishment of normal urinary secretion was later than in Group 1. The urine contained more albumin—usually 3 or 4 gm. per liter during the first few weeks. Traces persisted during the entire stay in hospital. Daily chlorid excretion and the response to the ingestion of extra

chlorids was poor, and usually caused the return of edema. Hematuria followed the salt test in two instances. Microscopic findings were as in Group I at first but differed in the degree and persistence of the cylindruria.

Phenolsulphone phthalein excretion was uniformly low early in the illness and frequently remained low after all acute symptoms had subsided.

Some impairment of the ability to concentrate was constantly present. Fixation of the specific gravity was usually at a high level—1.020. A relative fixation, variation of four or five points, and inability to raise that of the night urine to 1.030, was the rule.

The response to the ingestion of large amounts of water was its gradual elimination during the whole twenty-four hours. The diluting power of the kidney was only slightly below normal. Two cases showed no deviation from the normal (Cases 3 and 6). Both patients were children who had less edema than the others of the group.

The blood examination was of less value in determining the prognosis than the other functional tests, the results obtained being much the same as in Group I. The higher creatinin values found in two cases (Cases 2 and 3) were the only exception to this rule.

Chronic Cases.—Only two cases of chronic nephritis were encountered in this series (Table 3). One of these patients (A. J.) died as a result of an acute nephritis superimposed on the chronic condition, and is considered with the fatal cases. In the other case, an attack of pharyngitis was followed in two days by the passage of bloody urine, which was not diminished in amount. Examination proved the discoloration to be due to hemoglobin and not whole blood. Microscopically, the urine differed from that of the acute cases in the absence of much blood and large mononuclears, and in the presence of large numbers of all kinds of casts. The fatal case, mentioned above, also showed numerous casts in the urine. The child passed large amounts of pale urine; half of the total amount was voided during the night. The edema cleared up quickly. The blood pressure and eye-grounds were both normal. Secondary anemia was marked. Functional derangement was most evident in the greater increase in the noncolloidal nitrogen of the blood, the inability of the kidney to concentrate, or to excrete satisfactorily added salt in the diet. Water excretion was good, but there was some failure in the diluting power of the kidney.

Fatal Cases.—Seven cases of our series terminated fatally. One of these (W. S.) was a case of nephrosis following the administration of calomel over a period of one week. Septicemia was the immediate

TABLE 4.—FATAL CASES OF NEPHRITIS

Name, Age, Date of Admision	Day of Dis- ease	Tem- pera- ture	Edema	Eye- grounds	Urine				Chlor- ids	Mac. Blood	Blood Pressure		Con- centra- tion Test	Water Test	Phenol- sul- phone- phthal- ein	Added NaCl	Blood				Chlor- ids
					Amount	Specific Gravity	Albu- min	Urea			Sys- tole	Dias- tole					Non- protein N	Urea N	Urte Acid	Creat- inin	
1. A. W. 9 yrs. 11/10/19	60	99	+++	N	400	1.010	0.10	0	105	80	24.2	34.5	22.4	1.2	0.90	0.099	0.58		
	90	98	+++	..	1,000	1.020	0.25	0		
	91	98	++	..	381	1.020	0		
	93	98.4	++	..	458	1.016	0		
	110	98.8	++	..	550	1.021	1.05	2.32	0		
	115	99	++	..	670	1.020	1.20	2.04	0		
	116	99.1	++	..	800	1.016	1.20	3.20	0		
	117	98.6	+++	..	760	1.019	1.20	0		
	137	99.2	+++	..	340	1.020	0.30	0	0		
	140	99	+++	..	50	1.013	0.18	0	0		
	142	99.2	+++	..	0	0	0	0.004	+		
	145	98	+++	..	40	1.015	0.30	0	0		
	148	97.2	+++	..	0	0	0	0	0		
	149	96	+++	..	0	0	0	0	0		
	152*									125	90	16.6	173.0	158.6	...	8.01	0.125	0.625		
2. M. B. 8 yrs. 12/7/19	45	99	+++	NN	++		
	47	98.6	+++	..	510	1.021	0.35	0.816	++		
	48	100	+++	..	535	1.020	0.50	0.856	++		
	51	99	+++	..	582	1.013	0.50	1.830	+		
	55	98.6	++	..	510	1.020	0.40	1.82	0		
	75	98.6	++	..	390	1.020	0.02	1.13	0		
	86	99	+++	..	452	1.017	0.45	0.497	0		
	96	98	+++	..	330	1.017	0.40	0.99	0		
	98†										
	10	100	+++	N	30	1.014	0.50	++		
3. M. S. 9 mos. 3/25/21	12	100	+++	..	30	1.015	0.55	0	++		
	13	99	+++	..	30	1.015	0.55	0	++		
	102†										
	4										
4. A. W. 2 wks. 1/1/21	7	+	+	..	35	0.03	0.0108	0		
	8	42	1.026	0.02	0.0308	0		
	9§										
	9									140	90		
5. A. J. 9½ yrs. 2/9/21	3	99	+	..	380	1.018	0.20	0.209	+		
	4	98.6	+	..	250	1.024	0.30	0.30	+		
	7	100	++	..	310	1.022	0.70	0.209	+	180	100		
	9	99	+++	..	160	1.020	0.72	0.06	0		
	11		
6. D. P. 3½ yrs. 2/22/21	12*	101	0	0	0	0	0		
	6	103	?	0	0	0	0		
	9	103	1.010	0.0†	0	+		
7. W. S. 16 mos. 2/3/20	16*	100	+++	1.010	0.85	0	0		
	14										
	15†										
											

* Died. † Died at home one day after removal from hospital.

‡ Died after convulsion.

§ Died suddenly

‡ Died at home following general convulsions and aneuria.

cause of death in two cases (Cases 1 and 6). One child (A.W.), aged 2 weeks, was admitted because of muscular twitchings and was believed to have had a cerebral hemorrhage. This infant passed very little urine, and it contained both blood and casts. Its nasopharynx was markedly congested. Necropsy revealed the presence of inflammatory changes in the kidneys and the absence of any intracranial lesion.

Temporary improvement was noted in most of these cases. Relapses were frequent and of increasing severity. The blood pressure was raised in the four cases in which it was taken. One child (A. J.) with an acute nephritis superimposed on a chronic nephritis died with uremic convulsions and had a blood pressure of about 200 during the last week of life. Retinal hemorrhage was seen in two cases.

Functional Studies.—Early indications of the bad prognosis in this group were furnished by the response of the kidney to functional studies. Early fixation of the specific gravity and failure to concentrate was seen. The specific gravity was usually fixed at 1.018 or 1.020 at first, but showed a constant tendency to become more rigidly fixed at a lower level as the disease progressed. Failure to excrete large amounts of water, even in the twenty-four hours, was present in all cases. Uniformly lower excretion of phenolsulphonephthalein was found.

The creatinin nitrogen gives the most valuable indication of prognosis. The other nonprotein nitrogen bodies were increased but not to such an extent as to warrant giving a fatal prognosis. The high creatinin value in one case (M. B.) was first obtained during a period of clinical improvement.

Little time was allowed for work on the case of nephrosis, as the child died suddenly within twenty-four hours of admission. He was admitted with general anasarca and the history of its having developed subsequent to the administration of calomel. At its onset, the urine was found to contain much albumin but few cellular elements. At the time of coming to hospital, two weeks later, the albumin was less in amount and a few blood cells and casts were present. Typical nephrotic changes were seen in the sections of the kidney.

PATHOLOGY

The pathologic data were obtained from the five fatal cases which came to necropsy. Three cases of nephritis, one case of chronic nephritis and one case of nephrosis were in this number.

1. *Acute Cases.*—In the gross, these kidneys were deeply congested and slightly enlarged. The glomeruli stood out as minute points above the surrounding tissue. Histologically, the most striking changes were seen in the glomeruli, which were swollen, congested and the seat of

cellular proliferation. The tubules contained much blood and some casts. Degenerative changes in the tubules, particularly the proximal convoluted portion, were present. Evidence of early fibrotic change was noted in all cases. The interstitial tissue showed little abnormality.

2. *Chronic Cases.*—The kidneys were larger than normal. The surface was finely granular. Histologically, inflammatory changes in all stages were seen. Some portions of the kidney showed scarring with fibrosed glomeruli, flattened and degenerated tubular epithelium, while in other areas there was an acute intracapillary glomerulitis, with little or no scarring. Cellular proliferation in the interstitial tissue was more marked than in the acute cases. The patient, whose kidneys are described above, had had scarlet fever four years previously and was admitted to the hospital this time suffering from acute nephritis. A history of nycturia during the interval, and the passage of an unusually large number of casts in his urine was the only way in which he differed clinically from other cases of acute nephritis.

3. *Nephrotic Case.*—The kidney was only slightly enlarged, somewhat pale in color, the cut edges rolled out and the cut surface presented a mottled appearance, due to the presence of greyish areas. Histologically only slight inflammatory changes were seen in the glomeruli. Extensive tubular degeneration was present. The cells of the proximal convoluted tubules were flattened. Cellular debris filled many tubules. The interstitial tissue was a little oedematous.

PROGNOSIS

The prognosis in nephritis in childhood must be based on a consideration of all available data, both clinical and laboratory. In our series of cases, 50 per cent. of the patients have recovered without any evident impairment of renal function or general health. This statement is based on the condition of some of these children who attend the outpatient nephritic clinic nearly a year after their illness.

Clinically, the presence of marked edema, or the persistence of slight edema longer than a month, indicates a severe lesion. The amount of blood in the urine seems of little significance but its persistence a month or longer, or its easy return following slight infections or the taking of salt in the food, demands consideration. Patients with frequent relapses do poorly. A moderate rise of blood pressure, if maintained, is a bad omen.

Functionally, the fixation of the specific gravity and poor excretion of phenolsulphonephthalein after the disease becomes quiescent, furnish the most reliable guides to prognosis. Fixation at a high level, 1.020 or more is of less serious import than fixation at a low level. The excretion of 50 per cent., or less, of phenolsulphonephthalein in two hours was considered low.

Determination of the nonprotein nitrogen of the blood proves valuable in some cases. High creatinin appeared to be the most certain evidence of severity, 3 mg. per hundred cubic centimeters indicating a severe lesion, while cases with 5 mg. or over ended in death. Increase in the other constituents after symptoms of the disease had passed, were of value, but if they were only raised during the acute stage of the disease they were of little value in prognosis.

The elapse of sufficient time to determine the development of a chronic nephritis in those cases showing a tendency that way, has only occurred in two cases. These two patients attend the outdoor now because they are below par physically. The urine still contains small amounts of albumin, blood cells and granular casts. Secondary anemia is still present.

In the fatal cases, functional studies indicated the outcome before clinical symptoms did.

TREATMENT

On admission to hospital patients were put to bed and remained there in most cases until all evidences of acute nephritis had disappeared. The diet was restricted to 1,000 or 1,600 c.c. milk, depending on the age of the child. Milk was well tolerated in most cases and furnished a salt and fluid poor diet with insufficient protein to cause any increase in the nitrogenous constituents of the blood. Fluid intake was limited to 1,600 c.c. at the most, the large part being made up of milk. A more liberal diet, consisting first of cereals and milk puddings, and later vegetables, was given as soon as retained waste products were excreted. Protein was added gradually, when the disease became quiescent, until a maximum of 40 or 50 gm. was given when the patient was clinically cured. Fish or chicken first, later eggs and meats were allowed on alternate days. The diet was kept "salt free" throughout the stay in the hospital, and salt was allowed later only if the response to the additional chlorids had been satisfactory, and productive of no edema or hematuria.

The work of Howland and Marriott¹⁰ on phosphate retention as the cause of acidosis in nephritis, and the favorable reports of the administration of calcium salts on nephritic edema by Hülse,¹¹ led us to use calcium chlorid or lactate, in 5 gm. doses, four times a day, in the hope of influencing favorably those two symptoms. Edema apparently clears up more rapidly when either of these drugs is given. The lactate seems superior to the chlorid. Few of our cases gave clinical evidence of acidosis, and no difference was noted in this respect

10. Marriott and Howland: *Arch. Int. Med.* **18**:709 (Dec.) 1916; *Arch. Int. Med.* **22**:477 (Oct.) 1918.

11. Hülse: *Centralbl. f. Inn. Med.*, Leipzig, **41**: No. 25, 1920.

whether calcium salts were given or not. Stimulation of diuresis by the administration of small doses of digitalis was tried in a number of cases without beneficial results.

Hot packs were used at first, but the small loss of water determined by weighing the patient before and after, and the evident depressant action on the patient, led us to discard their use later. Hot stupes to the lumbar region appeared to be equally effective and less disturbing to the patient.

Exsanguination transfusions were done in two cases of uremia. In one of these cases complete suppression of urine had existed for four days previously and urinary flow was reestablished after the transfusion. Delay in getting a suitable donor for the other patient allowed him to become moribund before the operation so that the fatal outcome was not averted. Simple transfusion, done in two cases, proved the most effectual remedy for the ever-present secondary anemia.

DISCUSSION

Cases of acute nephritis in childhood may be divided into those cases in which apparently complete recovery ensues after from three to five weeks, and those cases in which improvement occurs for a time and then the conditions remains in statu quo; in other words, the resolving and the nonresolving types. This latter type frequently terminates fatally following a relapse or some intercurrent infection. Functional tests differentiate cases into these groups earlier and more surely than do clinical observations.

Hematuria.—Microscopically, blood was found in all cases. It was present in large amounts in the majority of instances. A tendency to recurrent hematuria was seen in a number of cases, and when present furnished contraindication to the phenolsulphonephthalein test, as this drug usually induced an attack. In three cases tonsillectomy caused the reappearance of this phenomenon. Hemoglobinuria, associated with the presence of a reducing body in the urine, was noted in two cases (M. G. and A. J.) without apparently any special significance. The blood sugar was normal in both patients.

Edema.—All degrees of edema, from slight puffiness under the eyes to general anasarca, were encountered. No patient failed to show it at some time during the illness. It was frequently the earliest sign noted, and was the most common cause of complaint by patients attending the outdoor clinic some months after the subsidence of the acute attack. Evidence of moisture at the bases of the lungs was not inconsistent with complete recovery, but in no case with general anasarca was the renal function restored to normal, and most cases exhibiting this sign ended fatally. No relationship between the plasma

chlorids and the degree of edema present was discernible. The suggestion of some authors that nephritic edema is dependent on acidemia may explain the favorable effects of calcium salts on edema, certainly they did not act by causing diuresis. In cases with troublesome edema, the administration of extra salt or water usually caused the edema to return.

Diuresis.—Normal urinary flow following the liguria was usually established by a steady, but often slow, increase in the urinary output. A number of therapeutic agents were employed from time to time but exerted no well marked diuretic effect. A definite and well marked diuresis occurred in only one case.

Uremia.—Vomiting of a severe and persistent type was the most common clinical manifestation of uremia. This phenomenon might be attributed to acidosis but it was unaccompanied by other manifestations of this condition and was accompanied by definite increase of nitrogenous elements in the blood. Alkali therapy proved of no value. General convulsions occurred in two cases, convulsive twitchings in one case. These three cases ended fatally. The uremia in most instances was asthenic in type. The blood pressure was high following convulsions.

Functional Studies.—The study of renal function furnishes at once the most reliable guide as to treatment and prognosis in nephritis. By this means a truer and earlier estimation of the gravity of the case can be made than by clinical observation alone.

The concentration test is one of the simplest and most reliable of these tests. In no acute case which recovered was there absolute fixation of specific gravity at any stage of the disease, while in other cases, comparable in other respects, its early fixation pointed to the nonresolving nature of the case. More severe functional incapacity, and consequently a worse prognosis, was indicated by fixation at a lower level.

The phenolsulphonephthalein test furnished invaluable information if done after the disease had become quiescent. Excretion of less than 40 per cent. in two hours at this state of the disease was only seen in those cases which tended to chronicity. Values below 25 per cent. were unusual and were found only in severe cases. However, excretion of normal, or nearly normal, amounts does not necessarily indicate a nonprogressive lesion.

The water test did not give such uniformly reliable results as did the concentration test. Very poor response early in the disease was frequently succeeded by normal response a few weeks later. Prognosis based on the excretion of large amounts of water is unreliable. Recurrence of edema followed the test in two cases.

Chlorid excretion furnishes a reliable indication of the progress the patient is making. An initial low chlorid concentration in the urine was present in all cases. No sudden outpouring of chlorids occurred in any case, but in cases tending to recovery the chlorid excretion gradually improved as the outflow of urine did. Traces only were found in some fatal cases. As a rule, the response to the ingestion of additional chlorids corresponded closely with that made to other functional tests, but tended to be worse in cases with much edema.

The estimation of the nonprotein nitrogen of the blood is of value when it is increased, but a normal figure did not always rule out kidney involvement. The urea nitrogen showed a proportionate increase in all cases. Creatinin values of more than "3" indicated severe damage, while those of "5," or over, warranted a fatal prognosis.

SUMMARY

1. The most common etiologic factor in nephritis is an acute infection.

2. Cases of nephritis in childhood may be divided into the following classes: (a) Acute glomerulonephritis, (1) resolving, (2) non-resolving; (b) chronic glomerulonephritis; (c) nephrosis.

The acute cases which recover are differentiated from the non-resolving type, by: (a) better response to renal function tests; (b) steady and rapid improvement clinically, and (c) rapid diminution and complete disappearance of the albuminuria.

The chronic cases differ in the history of past symptoms and signs attributable to the kidney, especially nycturia, in the presence of more numerous casts in the sediment.

3. Relapses occur frequently in the more severe cases, and of themselves justify a bad prognosis.

4. Tests of renal function give invaluable aid in determining the prognosis and line of treatment. The concentration test and the determination of the blood nitrogen constituents furnish the most reliable data.

5. Consideration of the response to functional tests coupled with clinical observation, enables one to foretell fairly accurately the outcome in individual cases.

6. Administration of calcium salts, particularly the lactate, is of definite value in clearing up the edema.

7. Pathologically, the most common lesion in the acute cases is a glomerulonephritis of the intracapillary type, accompanied by more or less degeneration in the cells of the convoluted tubules. The chronic cases showed the same lesions as the acute cases plus scarring and fibrotic changes. In the nephrotic case, tubular changes predominated.

ECZEMA IN BREAST FED INFANTS AS A RESULT OF SENSITIZATION TO FOODS IN THE MOTHER'S DIETARY*

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Eczema in breast fed babies has been even more puzzling to physicians than that occurring in the artificially fed, or in adults. Its etiology has been almost wholly a mystery; treatment has been empirical, and results have been as unsatisfactory as one would expect. Recent researches give promise of a rational explanation of the cause and a scientific method for the cure of the condition. It has been shown that breast milk may transmit foreign proteins derived from the foods of the mother and it is contended that these proteins are responsible for eczema in at least a large percentage of breast fed babies.¹ It is the purpose of this paper to offer further clinical support for this contention.

Since Czerney's work on exudative diathesis appeared his idea of disturbed fat metabolism as a cause of eczema in breast fed babies has dominated opinion largely.² Finklestein's "salt" theory gained little support.³ However, in eczema in artificially fed and older children opinion has diverged widely. Unquestionable cases have occurred in which thyroid deficiency has been a factor, and this has led to the formulation of theories based on disturbance of internal secretory mechanism as a cause.⁴ External irritation is considered as a factor by all. It is contended by some clinicians to be the main responsible cause.⁵ A disturbed vegetative nervous system has been offered as a cause in some cases.⁶ Indeed, Czerny recognized the frequent association of eczema with a disturbed nervous mechanism and attributed to some extent the degree of the condition to this complicating factor. Finally, the discovery of food anaphylaxis and the rapidly spreading understanding of its significance has led to frequent proof of its rôle in the causation of symptoms.⁷

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* From the Miller Hospital Clinic.

1. Shannon: *Am. J. Dis. Child.* **22**:223 (Sept.) 1921.

2. Czerny, A.: *Jahrb. f. Kinderh.* **61**:199, 1905; *ibid.* **70**:529; *Monatschr. f. Kinderh.* **4**:1, 1905; *ibid.* **6**:1, 1907; *ibid.* **7**:1, 1908.

3. Finklestein: *Med. Klin.*, 1907 (Quoted from Gerstenberger).

4. Edelman, M. H.: *Med. Rec.* **91**:303, 1917.

5. Simpson: *J. A. M. A.* **58**:995 (April 6) 1912.

6. Hazen: *Arch. Dermat. & Syph.* **1**:642 (June) 1920.

7. Blackfan: *Am. J. Dis. Child.* **11**:441 (June) 1916. Talbot: *Boston M. & S. J.* **179**:285, 1918; *ibid.* **175**:409, 1916. Fox and Fisher: *J. A. M. A.* **75**:907 (Oct. 2) 1920. White: *Boston M. & S. J.* **178**:5 (Jan. 3) 1918.

O'Keefe opened the way for a rational understanding of eczema in breast fed infants.⁸ He showed that "a large percentage of breast fed infants suffering from eczema show a positive cutaneous reaction to food proteins" and suggests that "foreign proteins occurring in the breast milk are the most probable means of such sensitization in this group of cases." He found that about 40 per cent. of these patients were cured by omission from the diet of the mother of the articles of food to which the infant was susceptible and that 20 per cent. more were definitely benefited.

Following on the work of O'Keefe, Shannon¹ demonstrated the presence of egg and veal protein in breast milk after their ingestion by nursing mothers.⁹ Strong clinical evidence was presented that the same might be true of almost any food that the mother might eat. Cases showing various exudative phenomena were presented and shown to be due to the presence of various proteins to which the infants were sensitive in the breast milk.

Aside from the papers referred to there is little mention in the literature of food anaphylaxis as a cause of eczema in breast fed babies. Talbot mentioned a case in which chocolate in the diet of the mother seemed to have been responsible for a severe eczema in an infant.¹⁰ Schloss mentions sensitivity to egg in artificially fed children who had never received egg in their diet.¹¹ They developed symptoms when fed egg protein. Occasionally, mention is made of the fact that the infant may be upset by certain foods that the mother may eat, but no mention is made of such foods being responsible for eczema.¹² Neither is the suggestion made that the protein of such food is the responsible factor.

Naturally, with ideas as to the etiology of eczema in breast fed infants so poorly formulated, treatment has not been satisfactory. For the most part it has been directed at the external factor, in itself not understood. What has been done in the way of internal therapy has been confined to the regulation of feeding with a view to cutting down the fat intake, as originally done by Czerny, or to the bolstering up of some imaginary incompetent mechanism of internal secretion.

The cases of eczema here reported occurred in either exclusively or essentially breast fed infants. Treatment was mainly dietary. Recourse

8. O'Keefe: Boston M. & S. J. **183**:569 (Nov. 11) 1921; *ibid.* **185**:194 (Aug. 18) 1921.

9. Shannon: Minnesota Med. **5**:137 (March) 1922.

10. Talbot: M. Clinics N. America, January, 1918, p. 985.

11. Schloss: Am. J. Dis. Child. **19**:433 (June) 1920.

12. Mulherin: J. A. M. A. **75**:855 (Sept. 25) 1920 (Discussion by Dr. Charles J. Bloom). Westcott: Am. J. Obst. **78**:55. Rotch: Pediatrics, 1901, p. 137. Griffith: Diseases of Infants and Children **1**:105, 1919. Colburn: Nebraska State M. J. **4**:243 (Aug.) 1919.

was had to external applications as a supplementary treatment in most cases. Several cases had shown no improvement during a preliminary period of external therapy alone.

Dietary treatment consisted in the removal of offending foods from the dietary of the mother and patient or their limitation. It was guided by the results of cutaneous protein tests performed on the infants. The technic of the tests was that described by Walker,¹³ with the exception that the infant's back was used instead of the forearm. Interpretation of the positive reaction was based on the occurrence of an erythema at the site of the test, as well as a wheal, as stated at a previous time.⁹

REPORT OF CASES

CASE 1.—Baby boy, 7½ months old, had eczema since 2 months of age. A reddened scaly eruption was present over the scalp, forehead and cheeks; marked papular eruption over left forearm and wrist, and to a smaller degree, over the right forearm and wrist.

Application of Lassar's paste for four days caused no improvement. Patient was tested with carrots, lima beans, lactalbumin, orange, cocoa, salmon, potato, navy bean, tomato, egg white, casein, wheat, pea, egg yolk, mackerel, rice, human milk, banana and pork, foods which were common in the diet of the mother, or which the infant had eaten. The infant had had cream of wheat, soda crackers, cow's milk and carrots. Positive reactions were obtained to carrots, lima bean, beef, banana, salmon, potato and pork, and questionable reactions to mackerel, rice, egg white and yolk.

External treatment was continued as before, and the mother was instructed to give the baby no more carrots and to eliminate from her own diet all pork, carrots, salmon, mackerel and banana. She was told to eat beef, egg, lima beans and rice no more than twice weekly, and to limit potato to one heaping tablespoonful daily.

Nine days later the hands and forearms were well. The scalp and right cheek were much improved but an impetigo had developed on the left cheek. This spread over the entire scalp and by the time this was cleared up, one month after the diet had been instituted, the eczema had disappeared, except for a slight scaliness over the left cheek and the forehead.

Two weeks later the patient returned. The mother said that until two days previously the skin had been perfectly smooth. At this time, concomitant with the cutting of two teeth, the rash had appeared on the scalp and the cheeks. Protein tests revealed positive reactions to spinach, which had not been tested before, and wheat, which had previously been negative. The infant had been receiving both these foods in his diet since the previous visit. Removal of these foods from the mother's and the patient's diets caused marked improvement in one week and disappearance of the eczema in one month. Since that time the baby has been weaned and is eating all of the foods to which he was sensitive, except carrots, lima beans and egg. The mother says that for a time slight palpable roughness would come and go on the cheeks. When last seen, six months after the first visit, there was no trace of eczema, although several teeth had erupted. The baby had been weaned and was doing nicely.

CASE 2.—Baby girl, 4 months old, was breast fed entirely, except for barley water. Eczema had been present since 6 weeks of age. When seen, a scaling eczema was present on the cheeks, chin, forehead, ears, neck, scalp and on the backs of the hands. The face was very red and angry looking, although there was no weeping or vesiculation. Over the back of the head the lesion was papular.

13. Walker: *Oxford Med.* 2:122.

The infant had already been on local treatment for two weeks, with continued progression of the eczema. Cutaneous tests were made with the following: food proteins—tomato, pork, grapefruit, chicken, egg white and yolk, veal, asparagus, barley, orange, oats, beef, wheat, rice, corn, casein; spinach, potato, peas, rye, banana and carrots. Positive reactions were obtained to egg white and yolk, rice, corn, potato, rye and carrots. Egg white gave both erythema and wheal. The remainder were only erythemas.

The mother was instructed to eat no eggs or food containing eggs, rye, or corn; to limit potato to two tablespoonfuls daily, and to limit carrots and rice to two tablespoonfuls twice weekly. Veal was to be eaten no more than once weekly. Lassar's paste was prescribed for the face and a mild scaling ointment for the scalp.

Very marked improvement had occurred in two weeks, which steadily continued with mild periods of exacerbation, until all signs of eczema disappeared five weeks after institution of treatment. One month later a slight scaliness was present on the cheeks which, the mother said, would come and go. At this time solid foods were added to the infant's diet. The mother did not return for a period of six months, during which time the infant had had no skin lesions of any kind. Within this period several teeth had erupted. The mother had completed the weaning and had come to restrict no foods but eggs. The mother herself had ceased her own dietary restrictions three months after the institution of treatment and no recurrence of symptoms had occurred in the infant.

CASE 3.—Baby girl, 5½ weeks old, was breast fed entirely. There had been no rash present on the skin until she was two weeks of age. At that time eczema had developed and it spread rapidly. The development of this condition was accompanied by considerable colic. When seen the infant had been on local treatment for one week with no effect on the course of the eczema. A very angry looking weeping and crusting eczema was present over the entire face and scalp and over the ears. Intertrigo was present in the folds of the neck. The skin over the buttocks was very irritated. The skin over the body was rough and reddened.

On questioning, the mother was found to be eating from two to five eggs daily. A sample of breast milk was obtained and egg protein was demonstrated to be present. The mother was told to omit all eggs or foods containing eggs from her diet. Lassar's paste was prescribed for the face. Eleven days later the mother reported that the condition was entirely clear, except for a little breaking out on the cheeks and slight crusting on the scalp.

Sixteen days later she returned with the story that two days previously the infant's face had begun to break out. When seen there was a papulovesicular eruption over the upper part of the face and forehead. The anterior part of the scalp showed a scaly eruption. At this time the infant was tested with lamb, oat, tomato, carrot, veal, egg white, grapefruit, peach, beef, egg yolk, casein, cauliflower, chicken, pork, barley, wheat globulin, lactalbumin, wheat gliadin, cocoa, wheat leucosin, beet, pea, rye, potato, cabbage, rice, banana, corn, human milk and celery. Erythematous reactions were obtained to veal, egg white and yolk, grapefruit, beef, chicken, barley, wheat leucosin, pea, rye, potato, banana, corn and celery. A questionable reaction was obtained to rice.

The mother was instructed to eat no egg or food containing egg, grapefruit, pork, pea, celery, banana, barley, or chicken; to eat beef, veal, wheat cereal, or rye cereal no more than twice weekly; to eat rye bread, and to eat sparingly of all wheat-containing foods.

Four days later there was considerable improvement of the eczema. However, the cheeks were still red at times and the forehead was rough and scaly, although not red. At this time I noticed that I had not restricted potato and the mother had been eating a great deal of this food. She was, therefore, told to eat no more than two tablespoonfuls three times a week.

Since this time there have been occasional appearances of rash on the cheeks in the form of what the mother calls "a few pimples," but most of the time the eczema has been absent entirely.

CASE 4.—Baby girl, 8 weeks old, was entirely breast fed. Eczema had appeared about three weeks previous. When seen a reddened, scaly eruption was present over the face, forehead and scalp. The skin over the back was roughened and scaly. Tests were made with coffee, beef, casein, individual wheat proteins, egg white and yolk, cabbage, oyster, human milk, grapefruit, tomato, pork, lactalbumin, rice, beet, salmon, potato, carrot, pear, orange, chicken, whole egg, oat, cauliflower, banana, veal, cucumber, pea, squash, strawberry, lettuce, cocoa and rye. Erythematous reactions were obtained to coffee, beef, wheat leucosin, pork, lactalbumin, salmon, rice, egg, potato, oat, pea, wheat proteose, cucumber and strawberry. The following restrictions were placed on the mother's diet: no coffee, beef, eggs, pea, salmon, cucumbers, wheat cereal, or white bread; no pork, except bacon or ham, and these infrequently; potato no oftener than four times a week; and rice, oranges, oats and strawberries no more than three times a week. Boil all milk and skim off the coagulum. Everything not mentioned could be eaten in unlimited quantity.

Two and one-half weeks later the mother reported that all skin lesions had disappeared, except a slight scaliness of the scalp. No local applications were used.

Eight days later the mother reported that the eczema had cleared up entirely at one time but that a few days previously the eruption had again appeared on the face. On close questioning she admitted that she had begun to eat some foods containing egg, and that she had begun to drink coffee. She was again cautioned not to eat these foods and nothing more was done. One month later the mother reported that all trace of eczema had disappeared promptly following the resumption of her diet, and that ever since the skin had been perfectly clear.

CASE 5.—Baby boy, 4 months and 1 week old, was breast fed entirely, except for orange juice and barley water. Eczema had appeared at 6 weeks of age, first on the scalp, and had spread later. When first seen there was a weeping and crusting eczema over the scalp and an angry looking scaly eruption over the face, neck and anterior surface of the trunk. The skin of the arms and legs was indurated and scaly. The infant had been under the care of a pediatrician for some time, in spite of which the eczema had spread. The infant was tested with corn, celery, egg yolk, rice, milk, carrot, wheat, tomato, peas, grapefruit, beef, casein, veal, barley, egg white, pear, asparagus, chicken, strawberry, cabbage, banana, oat, salmon, human milk, potato and pork.

Erythematous reactions were obtained to corn, egg white and yolk, grapefruit, milk and veal. Questionable reactions were obtained to chicken, wheat and cabbage. Two days later the egg yolk and grapefruit reactions were red, indurated and scaly.

The mother was taken off the foods to which the baby reacted. Improvement was very rapid for a period of five or six days, the mother said, when the infant developed a cervical adenitis and the eczema got worse. However, it did not revert to a condition as severe as when first seen. The abscess was opened and drained. The eczema remained stationary for a period of about two weeks, when the skin condition suddenly got much worse. The mother was instructed to pin the baby down on a hard bed and cover the body with Lassar's paste. This she did, and one week later the skin showed much improvement. On the day before this visit the mother said that a discharge was coming from one ear. From this point on improvement was steady. Further tests were done and positive reactions were obtained to beef, tomato, rice, rye and barley. These foods were restricted from the diet of the mother. Cod liver oil was added to the mother's diet. When last seen, twenty-five days after the ear had begun to drain, which was the last of a series of complications following a very severe nasopharyngitis, there was a slight roughness over the scalp and face. The skin over the anterior surface of the trunk was clear and the leathery condition of the skin of the arms and legs had largely disappeared.

CASE 6.—Baby girl, 4 months old, was breast fed. Eczema had appeared at 1 month of age and had become steadily worse. When seen there was a severe weeping eczema of both cheeks, papular eruption over the scalp, and scaly lesion on the chin.

Tested with egg yolk, barley, wheat, casein, cocoa, grapefruit, lactalbumin, corn, rice, veal, asparagus, strawberry, potato, chicken, banana, carrot, oat, pea, human milk and egg white. Positive erythematous reactions were obtained to egg yolk, casein, grapefruit, lactalbumin, strawberry, carrot, egg white, corn, rice, veal, asparagus, chicken and peas. Potato was doubtful. The mother had noticed that the baby had colic when she ate grapefruit.

Lassar's paste was prescribed for the face and the following restrictions were placed on the mother's diet: Eat no grapefruit, eggs, strawberries, veal or asparagus. Eat carrots, corn, rice and peas no more than twice weekly. Eat no more than two tablespoonfuls of potato daily. Eat infrequently of chicken. Take no more than one pint of milk daily and boil this for three minutes.

The baby developed mumps two days later, and the eczema spread over the body and arms. The back developed indurated and scaly patches around several of the positive tests. During the course of the mumps the eczema did not improve. As soon as the infant was well of the mumps she was put in the hospital where greater detail could be given to local treatment and control of scratching. Here the infant was placed on a hard bed with hands tied down and Lassar's paste applied to the entire body. In eleven days the child was discharged from the hospital very much improved. Five days later all that remained of the skin lesions was a slight seborrhea, a few papules on the neck, and some roughness of the cheeks. One week later a slight roughness of the cheeks only was present. Since that time an occasional roughness has appeared on one or both cheeks, but most of the time the skin is as clear as any baby's. At 10 months of age the baby was entirely weaned and is now, at the age of 1 year, taking all of the food that an ordinary baby of this age is given, with the one exception that all milk is boiled five minutes.

It is in the unfavorable case that theories are most rigidly tested. I therefore present the following cases which I should consider unfavorable, in order to analyze them from the standpoint of anaphylactic cause.

CASE 7.—Baby girl, 4 months old, was entirely breast fed. Eczema had appeared at 2 months and gradually spread so that when first seen there was a scaly, slightly crusted, angry looking eruption over the cheeks and scalp. A papular eruption was present over the diaper region, the outer aspect of the left leg, and in the left antecubital space. Blepharitis of both lids was present.

Cutaneous tests were made to coffee, pork, oats, salmon, egg white, rice, carrot, casein, cabbage, lactalbumin, peas, yolk, potato, human milk, wool, beef, veal, banana, wheat and orange. Erythematous reactions were obtained to beef, wheat, carrots, potato and banana. Egg white and casein gave both an erythema and a wheal. Orange and veal were regarded as questionable.

The mother was told to eat no egg or food containing egg. No more milk was to be taken than was necessary on cereal, etc., and this was to be boiled for three minutes.

The mother did not return with the patient for six weeks, during which time the eczema had improved greatly. There had remained, however, a slight scaliness of the cheek, a seborrhea of the scalp and some eczema on the arm. Two weeks before the second visit the eczema had begun to get worse, and when seen the infant was much worse than on the first visit.

The mother was instructed to continue the first restrictions and, further, to eat no beef, veal or banana. No wheat containing foods were to be taken except rye bread. Potato was to be eaten only three times weekly. Oatmeal was prescribed for the baby.

One week later there was marked improvement but there was still crusting on the cheeks. Two teeth had erupted.

The infant was then tested with human milk, rye, barley, wheat, peas, egg yolk, whole egg, lactalbumin, cabbage, oat, orange, veal, milk, rice, salmon and beef. Many of these had previously been negative, others positive or questionable, and still other foods were new. Whole egg and egg yolk gave both erythema and wheals. Milk and beef both gave an erythema. Veal, which had previously been questionable, remained the same. Wheat had been previously positive but was negative now.

The mother admitted that she had been eating white bread and store cake, which contained some egg. She was further instructed to eat no egg or food containing egg, no beef, and to drink as little milk as possible. She was permitted to eat a small amount of wheat bread, since she insisted that she could not eat rye bread.

Three weeks later the mother returned with the baby. There had been marked improvement in the eczema. However, she insisted that the baby had not been getting enough breast milk and that, therefore, she had begun feeding a complementary milk mixture and cream of wheat a few days before.

Because it seemed impossible to have the cooperation of the mother it was decided to allow her to continue the feeding of these foods to which the infant gave positive skin tests as an experimental procedure. Two weeks later the mother returned with the patient showing a marked exacerbation.

Cutaneous reactions were again repeated, with whole egg, banana, veal, lactalbumin, casein, potato, wheat globulin, beef, milk, carrot, wheat, wheat leucosin, proteose, gliadin, glutenin, salmon and egg yolk. Positive reactions were obtained to egg yolk, whole egg, banana, potato, wheat, wheat leucosin, carrots, veal and beef. Questionable reactions were obtained to several more of the individual wheat proteins. The mother admitted that she had of late begun to eat egg, banana, wheat, potato, beef and veal.

The mother was once again given instructions to eat no egg, banana, carrots, veal, or beef; to drink as little milk as possible; to eat potato only three times a week. The baby was to have oat, rye, barley or rice cereal instead of wheat, and to continue the milk mixture well boiled. Spinach and carrots were to be added at the 2 o'clock feeding.

Two months later the mother returned with the patient. During this time the eczema had been practically absent until one week previously. At this time a marked exacerbation occurred. This came with the cutting of two teeth and a bad head cold complicated by a double otitis media.

On close questioning the mother admitted that she had adhered to the diet for awhile but that of late she had restricted neither her own nor the infant's diet to the foods prescribed. I again cautioned the mother regarding the diets of herself and the baby and dismissed her.

In this case treatment was discontinued after a period of five months, with the eczema in just as bad shape as it was when treatment was started. During this entire time the patient was seen only six times. Three exacerbations occurred. At the time of each flare-up the mother admitted that a short while previously she had ceased to follow the dietary instructions given, and that she was either eating or feeding the baby the forbidden foods. After each visit there was a period of marked improvement, during which time the diet was adhered to, amounting to practically complete cure, according to the testimony of the mother. Two of the recurrences occurred at times of teething, when it is well known that eczema is likely to become worse. It is interesting to compare this point with Cases 1, 2 and 6, in all of which teething occurred without new outbreaks of the eczema after treatment

had been instituted. It is reasonable to assume that a strict adherence to the dietary regime laid down would have prevented the recurrences in this case as well.

The following unfavorable case is of interest from another point of view:

CASE 8.—Baby girl, 8½ months old; eczema had begun at the age of 2 weeks. The infant had been under the constant care of a pediatrician since that time, with no favorable effect on the eczema. The mother came in for advice as regards weaning, believing, as she had been told, that eczema was incurable and nothing could be done. Lately she had been giving a little cow's milk and had noticed that wherever this came in contact with the skin of the face around the mouth large welts appeared. Besides breast milk the infant had received cow's milk, carrots, spinach and cream of wheat.

When first seen there was a very angry looking, crusted eruption over the face, the forehead and the diaper region. The mother stated that at times it had been present over practically the entire body, but that just now it was improved.

Cutaneous tests were made for orange, lamb, asparagus, chicken, strawberry, celery, pear, spinach, wheat gliadin, cocoa, beef, wheat proteose, wheat glutenin, rice, cow's milk, carrots, navy bean, cucumber, wheat globulin, egg yolk, tomato, veal, whole egg, barley, cauliflower, human milk, lettuce, cantaloupe, wheat leucosin, cabbage, grapefruit, salmon, rye and oats. Positive reactions consisting of both an erythema and a wheal were obtained to wheat, wheat gliadin, wheat glutenin, wheat proteose, cocoa, rice, cow's milk, wheat globulin, egg yolk, whole egg, barley and wheat leucosin. Erythematous reactions were obtained to orange, lamb, chicken, celery, pear, beef, pea, salmon, cantaloupe, lettuce and veal. The controls were negative. There were thus only twelve out of the thirty-five proteins tried that were negative.

The following dietary restrictions were imposed on the mother: to eat no wheat cereal, rice, barley, tomato, celery, chicken, beef, salmon, pears, cantaloupe, cocoa, or chocolate. Asparagus, peas, beans, lettuce, potato, corn, veal and pork were to be eaten no more than once or twice weekly. Milk was to be taken only on cereal and this was to be boiled five minutes. Rye bread or rye crisp were to be eaten in place of wheat bread, although this contained 50 per cent. wheat flour.

The baby was to be given rye or oat cereal at the 10 a. m. and 6 p. m. feedings, and either spinach, carrots, or cauliflower at 2 p. m.

Lassar's paste was prescribed for local treatment. With this the mother was perfectly familiar.

Two weeks later the mother said there had been a marked improvement. Broths were then prescribed for the baby and the condition immediately got worse.

The infant was seen the second time, one month after the diet had been prescribed. At that time the cheeks were better than at the first visit, but much worse, the mother said, than they had been before broths were given to the baby. The skin over the diaper region was very much improved.

The diet of the mother was not changed. That of the baby was modified as follows: asparagus, peas, string beans, cauliflower and carrots were to be given, each in small quantity and not more than twice weekly at the 2 p. m. feeding, with rye and oat cereal as before. Lamb broth only was to be given, and that at the 2 p. m. feeding. Apple sauce and potato were to be added at 2 p. m. Nursing was to be discontinued at this hour. The attempt to get goat's milk was unsuccessful.

Sixteen days later there was some improvement in the eczema over the face. However, the cheeks were still rough and slightly red, while the buttocks had isolated spots of erythema. Instructions were given to add rye bread toast at 2 o'clock, and 3 ounces of milk boiled five minutes before the 10 a. m. and 6 p. m. feedings.

One week later the skin over the buttocks was normal. The cheeks were still rough and slightly reddened. The infant's diet was so altered that she should be nursed only at 6 a. m. and at 10 p. m. Three ounces of milk boiled five minutes were to be given at 10 a. m. No new vegetables, cereals, broths, or fruits were added, although the quantity was increased.

One month later the mother reported that the baby was much better. She was taking 4 ounces of the boiled milk, three times daily. The eczema had improved greatly and all evidence of the cold which the infant had had constantly since birth was gone.

Ten days later the skin of the face, legs and arms was still slightly roughened but not reddened. The infant was entirely weaned from the breast. The mother was instructed to give 4 ounces of boiled milk twice daily as a beverage, and to cook the cereal in milk. Cod liver oil was added in the form of 1 teaspoonful of the emulsion three times daily.

Four days later the mother returned with the story that the eczema had broken out afresh and that it was about as bad as it had been at the first visit. She was told to discontinue the cod liver oil and no further change was made. At the present time, five weeks after the cod liver oil was discontinued, the eczema is but slightly improved.

In this case also the eczema was almost as bad at the end of four months of treatment as it was in the beginning. However, such a result was anticipated on the first day. The infant was sensitive to the main articles of the mother's diet and should be weaned. In spite of the widespread sensitization, the anaphylactic property of the breast milk seemed to be decreased by limitation of the mother's diet sufficiently for marked improvement to occur so long as the infant was receiving only foods to which no reaction was obtained. When, however, beef, mutton and chicken broths were added to the diet of the infant, an immediate exacerbation resulted. Erythematous reactions had been obtained to all of these foods. Careful selection of foods permitted a gradual improvement of the eczema to progress along with the weaning process. However, when the infant was finally taken entirely from the breast, a severe recurrence resulted. The addition of the cod liver oil at this particular time was unfortunate. It may have been responsible indirectly for the outbreak. On the other hand, the recurrence might have occurred had the cod liver oil not been given. At any rate, its effect could only have been indirect since recovery was not prompt after its removal from the diet. Just before this outbreak the cow's milk in the infant's diet was increased. It is more probable that this increase overstepped the patient's tolerance for cow's milk and that, as a result of this mistake, the eczema recurred.

Eight cases of eczema in breast fed babies have been reported in detail. In all cases the main consideration in the study and treatment has been the anaphylactic reactions of the infant to foods contained in the mother's dietary. These reactions have been determined by the use of cutaneous tests done on the infants with the proteins derived from the foods that the mother has been eating. The interpretation of the positive reaction has been based on the occurrence of an erythema

at the site of the test, as well as a wheal. This is insufficiently emphasized by the majority of other observers in this field, and is very important. By far the majority of subjects give only erythematous reactions to the cutaneous tests, and if this type of reaction is not recognized in its full importance, results are bound not to be satisfactory. Of the cases cited four only gave a wheal in any reaction. Of these four cases, three gave a wheal to only one of the foods tested. The other case, having been a very severe one, gave a wheal at the site of the test with twelve different proteins. In Cases 1, 3, 4 and 7 return of the eczema can be traced quite definitely to the eating of foods to which an erythematous reaction only was obtained. Furthermore, some of the erythematous reactions in Cases 1, 5 and 6 remained for a period of from twenty-four to forty-eight hours, giving rise to scaly, eczematous patches before they disappeared.

Local treatment was used in almost all of the cases cited and consisted of the application of Lassar's paste to the affected areas whenever used. In several cases local measures had been employed for varying periods of time, without result before dietary measures were begun. In several of the cases in which exacerbations occurred the mothers had employed this treatment as soon as the rash had appeared and the local treatment had failed to check the progress of the eczema. On the other hand, it seemed to be of some value in combination with dietary treatment in minimizing external factors and thereby hastening cure.

Dietary treatment consisted in the removal of the offending foods or their limitation in the diet of the mother and patient. Certain foods, as eggs, were always eliminated. However, very frequently sensitization was so widespread that all foods could not be eliminated. In these cases the foods which gave the strongest reactions were eliminated so far as possible and the others were limited both as to quantity and the frequency with which they were eaten. It was thus very often impossible to remove entirely all of the offending foods from the diet of the mother. Particularly is this true when wheat is an offending food.

Sensitization in all of the cases tested was multiple. In one of the unfavorable cases no less than twenty-three different proteins gave definite reactions. In this fact is to be found the obstinacy of the disease. There are cases, however, in which a smaller number of foods is causative. The cases cited by O'Keefe,⁸ in which relief was obtained by the removal of one or two foods from the diet of the mother, are apparently of this type. It is not improbable that only a few of the foods to which an infant reacts are causative at any one time, and that, had we a method of determining which of the group these were, cure might be obtained by a less complete limitation of the diet of the

mother. However, for the present, it seems advisable to consider all foods giving a positive reaction in the infant as contributing factors, and to eliminate them from, or limit them in the diet of the mother.

Sensitization may occur to new foods throughout the course of eczema. This may give rise to new exacerbations of the disease. Flare-ups of this kind do not in any way weaken the theory, but rather strengthen it. If, on a new outbreak of the disease, we are able to demonstrate a newly acquired sensitization, and are able again to cause a disappearance of the symptoms by removal of these foods from the mother's diet, it would seem more certain than ever that foods were responsible. Such a phenomenon occurred in Cases 1 and 5. This observation brings up an important point in the management of these cases. The mother should be cautioned to eat a large variety of foods and a small quantity of individual foods. It seems that this would militate against further sensitization and is advisable as regards foods to which the infant is not sensitive, as well as those to which a reaction has been obtained but which could not all be eliminated from the diet.

Failures will continue to occur in this method of treatment as in any other. These may be explained in any one of several ways. First, it is essential to have the complete cooperation of the mother. Case 7 is an outstanding example of failure to effect a permanent cure on account of the lack of such cooperation. In this case almost every return of the eczema was occasioned by the fact that the mother had ceased to live up to the requirements of the diet prescribed. Each time she returned and was again encouraged improvement resulted until she again gave up to her appetite, when the disease once more broke out in the infant. In Case 4 the return is explained in the same way. Second, sensitization may be so widespread that it is impossible to prescribe a sufficiently liberal diet to mother or patient without utilizing some of the offending foods. Case 8 was such a case. Even in this case improvement occurred up to the point where it seemed necessary to add the offending foods to the diet of the infant. Third, failure on the part of the physician to test with all the foods may result in failure to effect a cure because of the fact that all of the offending foods may not have been eliminated. Case 1 illustrates this point. Spinach was not tested at the first visit because the mother did not eat it. It was prescribed for the baby and when, six weeks later, an exacerbation occurred, the infant was found to be sensitive to this food. O'Keefe would unquestionably have obtained a larger percentage of cures had he tested with a larger variety of foods and limited the mother's diet accordingly. Fourth, sensitization to new foods may occur and prolong the disease, as in Cases 1 and 5. Fifth, failure may occur as a result of unavoidable sources of error in the skin tests. Difference in technic

and interpretation will undoubtedly account for many of these errors. However, given a uniform technic and an identical interpretation, errors are bound to occur. Walker has shown that negative skin tests may be obtained to foods to which an individual is sensitive if the individual has not been eating that food for some time.¹³ Schloss has shown that after a severe outbreak of urticaria following the ingestion of an offending food the skin test may disappear for a period of a few weeks.¹¹ An example of this latter type of reaction occurred in Case 7. On the first test the infant was sensitive to wheat. Following an exacerbation of the eczema, preceding which the mother had been eating cake and white bread, the reaction to wheat was negative. Tested again several weeks later the reaction to wheat was again positive.

Czerny² and others have called attention to the fact that intercurrent disease is prone to have an unfavorable effect on the course of an eczema. He even advises against vaccination in these cases for this reason. Intercurrent disease giving rise to general manifestations occurred in two of these cases. It is of interest that these two were the most resistant of the favorable cases. Case 5 improved remarkably for a period of six days after the mother had been instructed as to her diet, when a severe nasopharyngitis, complicated by a cervical adenitis, developed. The eczema immediately reverted to somewhat of its former condition, although to a lesser degree. The adenitis was followed by an otitis media and definite improvement of the eczema did not again occur until after the ear had begun to drain. From that point on improvement was rapid for a period of twenty-five days, after which the patient did not return. Case 6 developed mumps two days after institution of treatment and the eczema spread over the entire body. On recovery from the mumps the patient was placed in the hospital in order to give attention to local treatment, and because the parents, not understanding the effect of the general condition on the eczema, were becoming impatient. From this point on improvement progressed rapidly to permanent cure. Had it been possible to eliminate all of the offending foods from the dietary of the mothers in these cases, we should expect not to have observed these severe exacerbations. However, this was not possible because of the widespread sensitization. Furthermore, Case 5 had become sensitive to several new foods in the interval.

The effect of teething on the recurrence of eczema is well known. Case 1 shows this point well. A repetition of the protein tests showed sensitization to two foods that the infant and mother were eating. Sensitization to one of these foods had occurred since the previous tests were made. The other had not been tested. Removal of these foods from the mother's and patient's diets caused prompt disappear-

ance of the symptoms. Since that time there has been no recurrence of the eczema in this patient at times of teething. Cases 2 and 6 also have had no recurrence of their eczema at times of teething.

A point of considerable practical importance arises in the question: when is it safe for the mother to resume her general diet, and when is it going to be possible for the infant to take the foods to which he has been sensitive after he has been weaned? Several of these cases have been followed long enough to throw some light on these questions. In Case 1 potato was added to the infant's diet two and one-half months after the mother had been restricted, without return of the eczema. Six months after the diet of the mother was instituted the infant was placed on a general diet for a child of its age, except that lima beans, carrots and eggs were withheld. There has been no recurrence of the eczema. In Case 2 the mother ceased her own dietary restrictions about three months after the diet was instituted, without recurrence of the eczema in the baby. One month later potato was added to the diet of the infant without bad results. In Case 6 the child was allowed to eat the foods to which she had been sensitive four months after the diet had been imposed on the mother. In Case 4 the eczema recurred when the mother resumed eating restricted foods one month after the restrictions were imposed. From these few cases it would seem that it might be possible for the mother to begin resuming her general diet after about three months, and that after a period of from four to six months it is safe for the infants to take the foods to which they have been sensitive. I feel certain that the result in Case 8 would not have been unfavorable if I had held off on weaning for a sufficient time, adding to the baby's diet only those foods to which she had shown no reaction and permitting her to receive her necessary quota of milk from the mother.

A study of this kind cannot but force on one a consideration of what might be done to prevent this malady. From what has been said it is seen that the nursing mother should be cautioned to eat a large variety of foods and a small quantity of individual articles of diet. Eggs, because of their frequent concern in this disturbance, should not be forced but rather restricted. Unquestionably some persons acquire their sensitization for some foods before birth, but in the majority this sensitization is acquired after birth through the breast milk. There is every reason to believe that in infantile eczema, as in protein sensitization in older children and adults, sensitization becomes more widespread as time goes on. It therefore behooves us to study these cases early and to try to eliminate the offending foods before sensitization has become so universal as to make their limitation a hardship, or even an impossibility. It seems reasonable that it might hinder further

sensitization, in view of the frequent intestinal upsets in these cases, which Schloss has shown predispose to absorption of undigested protein.¹⁴

CONCLUSIONS

The foregoing study permits of the following conclusions:

1. Eczema in breast fed babies is a result of sensitization to food proteins contained in the mother's dietary and transmitted to the infant through the breast milk in at least a great majority of cases.

2. Removal of these proteins from the diet of the mother usually results in cure of the condition in the patient.

3. In cases in which all the foods cannot be eliminated from the diet of the mother, limitation of the same will often result in improvement of the eczema, presumably because there is a threshold in the mother up to which the food may be eaten without appearing in the breast milk.

4. Sensitization of the infant may be determined by the cutaneous reaction to the purified food proteins.

5. The erythematous reaction at the site of the test is to be considered as indicating sensitization, and being much more common than the wheal, is correspondingly more important.

6. Sensitization is usually multiple and may be to a majority of the foods in the dietary of the mother.

7. Sensitization tends to become more widespread in a great many cases as time goes on, due to the acquisition of sensitization to new foods.

8. Repeated exacerbations and failures to cure may be due to (a) a lack of cooperation on the part of the mother; (b) sensitization so widespread as to make sufficient limitation of diet impossible; (c) failure on the part of the physician to test for all of the foods; (d) the acquisition on the part of the infant of sensitization to new foods, and (e) errors in the procedure of determining sensitization whether avoidable or otherwise.

9. As general prophylactic measures it is recommended that all mothers be cautioned to eat a large variety of foods and a small quantity of any individual article of diet, that eggs be restricted rather than forced in the diet of the mother, and that all cases of eczema be studied early and offending foods eliminated before sensitization becomes so widespread as to make proper limitation of diet impossible.

10. The proper study of all cases of eczema in breast fed babies that do not yield promptly to the older methods of treatment requires the determination of sensitivity in the infant to all of the foods contained in the diet of the mother and, in the event of exacerbations, the frequent repetition of these tests. Until the physician has done this he cannot be considered as having done his whole duty to the patient.

14. Schloss and Worthen: *Am. J. Dis. Child.* **11**:342 (May) 1916.

SITTING-HEIGHT AND STEM-LENGTH IN PRIVATE SCHOOL BOYS *

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Reason for Studying These Measurements.—As a gage of build, the hitherto honored standard of stature (standing-height, H) is equaled or excelled by the "essential stature" (the body-trunk, measured by different observers from slightly different landmarks, e. g., sitting-height, Si , or stem-length, λ). Evidence for this statement has been exhibited in recent papers¹ on the relation between these three body-measurements (H , Si , λ) and body-weight.

A new interest, therefore, arises in standards of sitting-height and of stem-length for children at successive ages. For the former (Si) tables already exist, but only (with rare exceptions) for children (1) of mixed nationality, (2) in public schools, and (3) without exclusion of those clinically below par. For stem-length (λ) no tables have been found in the literature.

The motive of this paper accordingly is the offer of tentative standards of sitting-height and especially stem-length for children: (1) of American birth and, indeed, of pure American stock (so far as such a thing can be found); (2) in private schools, i. e., in children of the best-fed and most carefully developed kind, and (3) after rejection of children subnormal to physical examination.

The data presented here, then, are supplementary to the tables (height for age, chest-girth for age, weight for height, and weight for chest-girth) which have been tentatively offered² as "Ideal," to distinguish them from the usual averages on mixed material.

New Material.—The subjects studied were 114 pupils at Mr. Robert W. Rivers' Open Air School for Boys, a country day school in Brookline, just outside this city. I am grateful for the opportunity to the principal and also to the school physician, Dr. Richard M. Smith.

From the latter's two recent studies on this establishment,³ it may be seen that the subjects represent a favored group, of American birth, good breeding in the broadest sense, and careful nurture.

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1. Gray, H., and Root, H. F.: Boston M. & S. J. **184**:439 (April 28) 1921; Ibid **185**:28, (July 7) 1921; Gray, H., and Walker, A. M.: Am. J. Physical Anthropology **4**:231 (July-Sept.) 1921; Gray, H., and Edmands, G. H.: Am. J. Dis. Child. **23**: to be published (March) 1922.

2. Gray, H.: M. Clin. N. America **4**:1899 (May) 1921; Gray, H., and Jacomb, W. J.: Am. J. Dis. Child. **22**:259 (Sept.) 1921; Gray, H.: Am. J. Dis. Child. **22**:272 (Sept.) 1921.

3. Smith, R. M.: A Health Study of a Boys' School, Am. J. Dis. Child. **18**:246 (Oct.) 1918; A Twenty-Four Hour Schedule for Schoolboys, Am. J. Dis. Child. **20**:115 (Aug.) 1920.

Furthermore, the subnormal samples of boyhood discoverable in process of betterment in every school have been in this study sifted out by means of the past history as obtained from parents, the physical examination by the school doctor, by irregularity in school attendance, and by general lack of stamina as observed from day to day by the school nurse in constant attendance.

TECHNIC OF MEASUREMENT USED HERE

Standing-Height.—The stature was measured to the nearest half-centimeter, with the subject barefoot and firmly erect, with head, shoulders, hips and heels against a wall; not in the frequent rather slack position against the rod attached to weighing scales. The former procedure seems to be that most approved in the literature, and has recently been the subject of the following comments:

Affleck ⁴ in 1920 stated that some observers advocate attempting to secure the "habitual" standing posture, but that in his experience much more uniform results are obtained by having the pupil "stand tall" or "stretch up"; and he added that "this is the one test in which encouragement of the pupil to do his best may be advised."

Wilder ⁵ in 1920 made another point: "As a purely academic question the arguments seem about equally balanced, with possibly a little more weight upon the side of the horizontal position; yet the arguments against this position are so cogent from a practical standpoint that at the International Congress of 1912 at Geneva the upright position was adopted as a part of the prescription."

Sitting-Height.—A box was placed against the wall. Each boy, stripped, was asked as he sat down to lift his hips well back against the wall, and, if his heels were not on the floor, to slip his feet forward. The purpose of this was to relax the leg muscles and thus approximate as nearly as possible, within the directions usually given for sitting-height, the rule for stem-length. In spite of this effort, the sitting-height proved inconstant as will be shown later.

Stem-Length.—For this we obeyed the enjoiner of Walker in 1916 ⁶: The length (λ) is measured by seating the subject on the floor or on a low table (not a chair) with the back against the wall. Care is taken to see that the sacrum is in contact with the wall, and the legs somewhat drawn up, so that the individual sits fairly upon his ischial tuberosities. Under these conditions the height of the top of the head gives a true measurement of the length of the body, and one

4. Affleck, G. B.: Pedagogical Seminar 27:324 (Dec.) 1920.

5. Wilder, H. H.: A Laboratory Manual of Anthropometry, Philadelphia, 1920.

6. Walker, E. W. A.: Proc. Roy. Soc. Lond. B 89:157 (Jan. 1) 1916.

which is constant and incapable of variation by the subject. If a chair or other form of seat be employed in taking this measurement the individual can by "sitting low" or "sitting high" produce at will a variation of as much as 3 or more per cent. But, since a subject conscious that he is being measured for height tends naturally to produce a full measurement, it will be found that he intentionally "sits up," straightening the spine, tilting the pelvis forward, and rests on the contracted muscles of the thighs and buttocks instead of on his ischial tuberosities. The apparent length—"sitting height," as it has been termed—is thus increased by between 2 and 3 per cent. above the measurement taken in the manner already described. Accordingly, measurements taken on a seat require to be corrected down appropriately before they can be treated as comparable with the measurements of body length in infants or animals.

A useful complement is the following abstract from Dreyer and Hanson⁷: The subject places the backs of the fingers on the platform on which he sits, and, with the fingers pointing backward and the knees flexed, lifts the lower portion of the body gently backward until the lowest bony portion of the os sacrum is in contact with the front of the measuring standard. The back is then straightened until the back of the head comes into contact with the standard. It will be found that different persons require to bend the knees in different degrees in order to achieve this position. The head should be tilted neither up nor down and the eyes should look straight forward.

For the present study these measurements were made personally, but though unusual, they seem practicable in any school, judging both by our own and by the more extensive experience of Porter⁸ in 1893, who wrote that the larger part of the measurements were made by teachers, whose hearty cooperation and efficient service in this work should earn them the gratitude of every friend of science.

TECHNIC OF MEASUREMENT USED BY OTHERS

It is very important to determine the best of the many possible trunk lengths, according to Wilder;⁵ and he added that "the symphysis (pubis) does not give full value to the physiological trunk, since it omits the lower part of the pelvic girdle, which should be included down to the plane of the sciatic tuber or the end of the coccyx. At present . . . the choice rests much in favor of the tuber."

This inferiority of the symphysis pubis as a landmark is supported by evidence recently published. Measuring to the sciatic tuberosities, as urged by Walker, Dreyer, Hanson, and Wilder, I think is the most

7. Dreyer, G., and Hanson, G. F.: *The Assessment of Physical Fitness*, London, 1920; reprinted by Hoeber, New York, 1921.

8. Porter, W. T.: *Tr. Acad. Sc., St. Louis* 6:249 (Nov. 14) 1893.

accurate practice. But even this measurement has been confused by the different technic used by sundry observers. Most have measured the sitting-height on a stool or bench in roughly (but not exactly) the same manner (e. g., Porter 1893, West⁹ 1894). Koganei¹⁰ seated his subjects with legs crossed in Turkish fashion, thus obtaining values said to be smaller by several centimeters than values with the stool method.

A few have specifically measured the stem-length (only Walker, Dreyer and Hanson, Gray and Root¹).

Wilder has clung to the term sitting-height as used by most observers but has defined a technic which differs from theirs and in fact seems to correspond to stem-length. His technic therefore conforms to our ideal of precision but his change in usage of the term sitting-height is to be deplored. So also is Dreyer's preference to stem-length of the old title trunk-length, because that name, though used since Sappey's paper was published in 1875 for the "central portion of the body," has been measured in such a variety of ways.¹¹

To illustrate, Porter took the height-sitting as the height from the crown of the head to the chair on which the child sits erect. West in his well-known investigations was slightly more particular, with the individual sitting pretty well back on a flat chair, the arms folded on the chest, the trunk erect. Hrdlicka¹² went a step further in exactitude: the height from the floor of the bench is most serviceably 50 cm., for shorter people and especially children the bench must be lower, the aim being for the thighs of the subject to be flexed at right angles to the trunk.

When measured with a bench from 30 to 40 cm. high, according to the 1912 Geneva agreement, as given in the official report by Duckworth,¹³ the sitting height more nearly approximates the stem-length.

Finally, the sitting-height most nearly approximates the stem-length, and may, indeed, be identical, when measured with the knees bent up, as apparently done by Godin¹⁴ (Busté = Vertex à ischion), by Ranke¹⁵ (Si = tubera ischiadica bis Scheitel), by Mall¹⁶ (1907) (crown-rump), and by Wilder (sitting-height): the subject should be seated on a low,

9. West, G. M.: *Arch. f. Anthropol.* **22**:13, 1894.

10. Koganei, Y.: *Mitth. a. d. med. Fac. d. Kaiserlich-Japanischen Universität, Tokio* **2**:256, 1894.

11. Sappey, P. C.: *Traité d'anatomie descriptive*, Paris, Ed. 3 **1**:4, 1875.

12. Hrdlicka, A.: *Anthropological Investigations on One Thousand White and Colored Children of Both Sexes, The Inmates of the New York Juvenile Asylum*, New York, 1899.

13. Duckworth, W. L. H.: *Am. J. Physical Anthropology* **2**:61 (Jan.-March) 1919.

14. Godin, P.: *Recherches anthropométriques*, Paris, 1903; *Bull. et mém. Soc. d'anthropologie de Paris*, S. 6° **1**:268 (June 16) 1910.

15. Ranke, O.: *Ztschr. f. Schulgesundheitspflege* **18**:719, 734, 816, 1905.

16. Mall, F. P.: *Anat. Rec.* **1**:128 (Aug.) 1907.

level table If the feet be placed on a rather high chair, thus lifting the dorsal muscles of the thigh from contact with the table, they cannot be used by the subject in lifting the body, while it rests directly on the sciatic tubers (ischadic tuberosities), here quite subcutaneous.

In the interest of lucidity it seems to me essential to realize that (1) Sitting-height has not been a uniform measurement because it has in general included a considerable but variable (a) thickness of buttock muscle, and (b) curvature of the spine; (2) stem-length is a uniform measurement because it includes a minimal and (on repeated observations on the same subject, even by different observers) surprisingly constant (a) muscular layer and (b) erectness of the spine.

It is, therefore, necessary to discriminate sharply between sitting-height and stem-length, as will be seen in Chart 1 on the difference between the two measurements in the present series of 114 boys.

METHODS USED HERE TO PRESENT DATA

Averages.—The individual cases are omitted to save space and the only value shown is their average (arithmetic mean) for each age-group.

Within each group, however, variability is to be expected. While a measure of variation is eminently desirable, the coefficient of variation (C.V.) and even the range (according to Yule¹⁷ a much inferior measure of variation) have not been listed here, owing to the relatively small number of subjects in each group. This calculation (C.V.) must be left for some observer with a larger series of observations at his command.

Absolute and Relative Measurements.—Physical measurements are frequently examined in two ways: actual values and proportional values. In conformity with this practice, the present new data will be shown first as (averages of) the absolute figures for each age, then as the ratios (indices) sitting-height to stature ($Si:H$) and stem-stature (λ/H).

The term "essential stature" has been credited to René Collignon of the French school (reference not discovered) by Montessori.¹⁸ Regarding the index of stature (Si/H) the latter authoress gives the following summary: "The essential stature very slightly exceeds 50 per cent., oscillating between 53 and 54; yet it may fall to 47 or even lower, or it may rise above 56 Hence, we may distinguish the type of stature by the name of brachyscelous (Manouvrier) when

17. Yule, G. U.: Introduction to the Theory of Statistics, London, Ed. 5, 1919, p. 133.

18. Montessori, M.: Pedagogical Anthropology, Translated from the Italian by Cooper, F. T., New York, 1913, p. 84.

the trunk is preponderant; and when the type is the opposite, that is, with long legs, by the name of macroscelous; reserving the term mesatiscelous to designate the intermediate type." Montessori goes on to discuss these types of stature according to total stature, to race, to social condition, in art, and in the two sexes.

COMPARATIVE SITTING-HEIGHTS AND STEM-LENGTHS IN ONE
HUNDRED AND FOURTEEN BOYS

The general relationship between the sitting-height and the stem-length is visible in Chart 1, where the stem-length is assumed to be

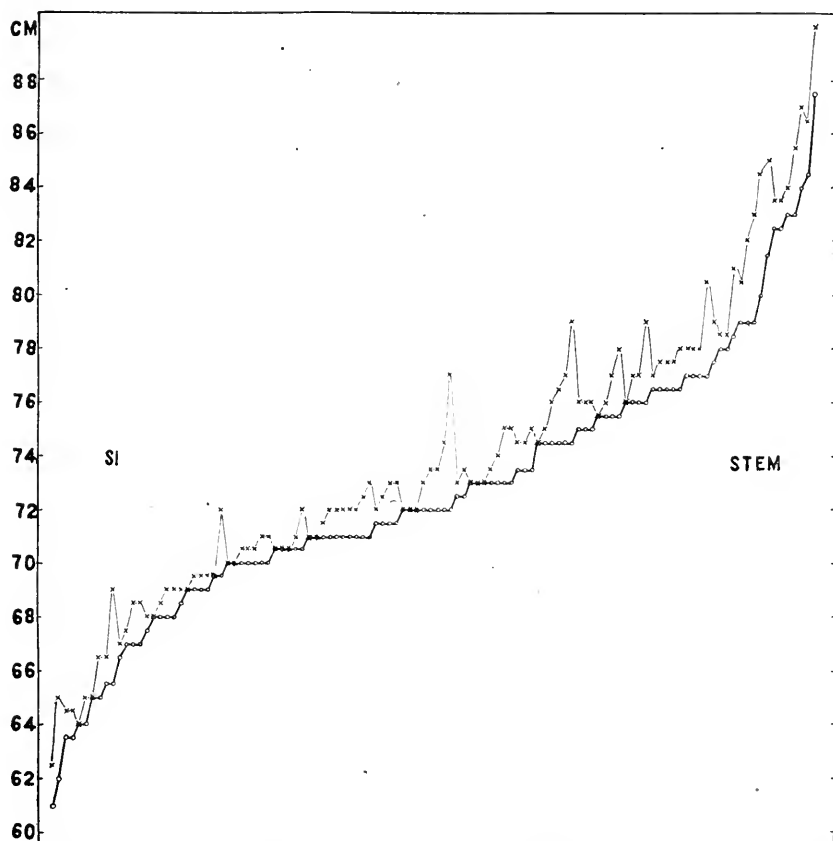


Chart 1.—Comparative sitting-heights and stem-lengths in 114 boys.

the standard value and the 114 cases are plotted seriatim from left to right, beginning with the smallest at the left.

The vertical scale of centimeters shows the size of the actual measurements of stem-length (0), and the sitting-heights (x) corresponding, i. e., those of the same subjects.

The following conclusions are obvious:

1. The sitting-height as measured in the usual way with the thighs horizontal, is never less than the stem-length, seldom equal, and nearly always greater.

2. The difference is inconstant.

This difference may be analyzed more accurately numerically in Table 1, which shows that the modal (commonest) divergence was

TABLE 1.—DIFFERENCE BETWEEN SITTING-HEIGHT AND STEM-LENGTH IN ONE HUNDRED AND FOURTEEN COUNTRY DAY SCHOOLBOYS (RIVERS SCHOOL)

Difference in cm.	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0
Number of boys showing difference named	21	21	33	16	5	7	4	3	1	2	1

1 cm., the average 1.2 cm., and the range of the divergence was from 0 to 5 cm. This two-inch difference is startling. Of the fact I feel certain, for I measured the stem-length directly after the sitting-height, and whenever the difference was less than 0.5 cm. or more than 2 cm. I repeated both measurements.

Sitting-Height (Absolute).—The average sitting-height for each age ("birthday norm") is shown in Table 2.

TABLE 2.—ABSOLUTE VALUES IN CENTIMETERS FOR SITTING-HEIGHT AND STEM-LENGTH

Age Nearest Birthday	Number of Boys	Sitting Height		Stem-Length	
		Smedley	Gray	Gray	Ranke
6	3	62.4	63.8	62.3	60.0
7	6	64.7	66.8	65.9	62.9
8	16	66.8	69.7	69.2	64.8
9	19	68.8	71.6	70.6	66.0
10	16	70.6	73.2	72.5	68.9
11	19	72.1	74.2	73.2	70.2
12	13	73.8	76.8	75.5	71.2
13	10	76.2	77.7	75.6	73.6
14	3	79.2	78.5	75.8	76.0
15	4	82.2	83.9	81.1	78.5
16	3	85.4	84.5	81.0	
17	(1)	88.2	(90.0)	(87.5)	
18	(1)	90.3	(87.0)	(84.0)	

In recording the ages the nearest birthday was used here as in previous studies. It has accordingly been necessary, when abstracting for comparison the results of other writers, to adjust those results if originally tabulated according to the last birthday. This adjustment has been speculative in some cases when the writers did not specify which birthday they used.

Comparison of the new averages with some collected from the literature is interesting. The new averages run about 2.4 per cent.

above those of Smedley¹⁹ which come the nearest and are therefore also presented in Table 2. Smedley's seem to be the only figures on the class in question—American private schoolboys. The other authors' series correspond in approximately the following order: nearest West, then Hastings,²⁰ Peckham²¹ (pure American but class not clear), Bertillon,²² Porter, and Hrdlicka.

For graphic comparison the values of these seven prior observers were charted, but the curves intertwined so bewilderingly that on the score of clearness the plotted points were pricked through on to another sheet (Chart 2). The dots were then blackened, tracing paper was laid

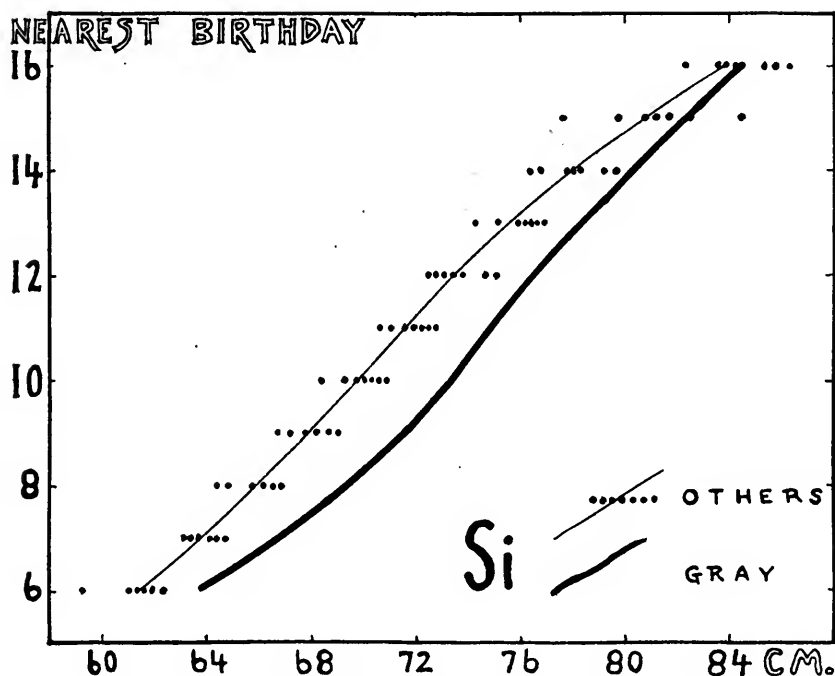


Chart 2.—Sitting-height for age.

on and a smoothed curve was drawn. Using two fresh tracing sheets, two more curves were sketched by independent observers. These three smoothings were then overlaid and as they nearly coincided, a composite was easily drawn by the eye and was then transferred also to

19. Smedley, F. W.: Forty-Sixth Annual Report, Board of Education, Chicago, 1900, p. 47.

20. Hastings, W. W.: Manual for Physical Measurements, Springfield, 1902.

21. Peckham, G. W.: Sixth Annual Report, State Board of Health of Wisconsin for 1881, Madison 6:28, 1882.

22. Bertillon, A.: Annuaire statistique de la ville de Paris, for 1887. Published 1889 10:856.

Chart 2. This free-hand procedure, while not mathematically exact, as discussed elsewhere,² is adequate to illustrate the general trend of a field of plotted points.

In Chart 2 the composite for the prior observers is shown by the light line, while the heavy line represents my new averages.

Two deductions are plain:

1. Individual earlier observers (black dots) differ relatively little from one another. It must be remembered (a) that the extreme right hand dots on each line do not all belong to one curve and the extreme left dots to another (which would indeed indicate a difference between

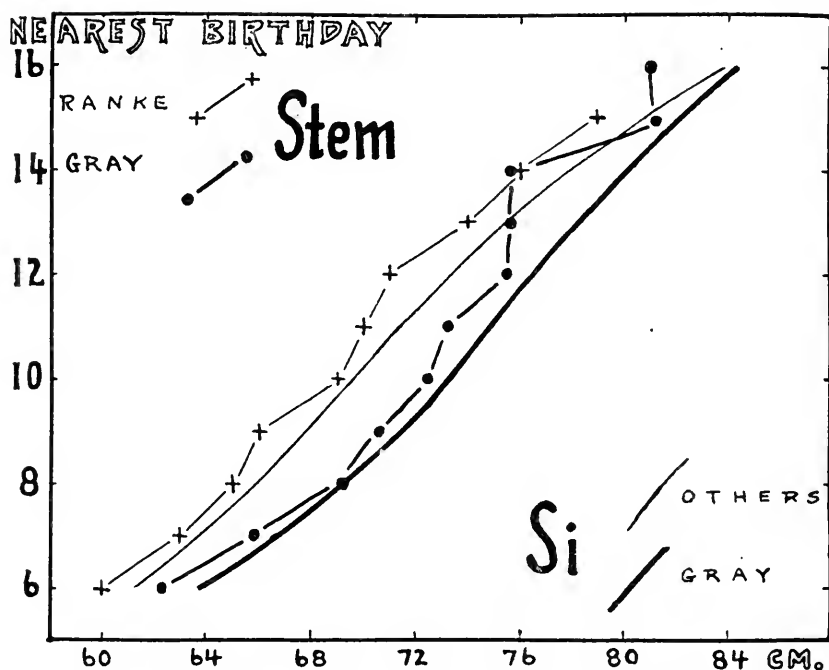


Chart 3.—Stem-length for age with, for comparison, the sitting-height curves from Chart 2.

them as great as the difference between the right dots and my heavy line), but (b) that the curves interlace almost inextricably.

2. The average of prior observers (thin line) differs notably from the new values (thick line). The latter sitting-heights are greater except at ages 15 and 16 years.

Stem-Length.—The actual stem-length for each age is averaged in Table 2. Graphically these averages are reproduced (heavy dot-dash line) in Chart 3. For comparison, the literature appears to afford no stem-lengths. Still the measurements of Ranke, 1905, were supposed

to represent the distance vertex to tuberosities, and, therefore, may be considered the nearest comparable values. So they also are given in Chart 3 (cross-and-dash line), together with the precise sitting-height line from Chart 2 (for contrast drawn as smooth curves instead of broken lines).

The lesson of the chart is that private schoolboys show a markedly greater stem-length than do Ranke's,⁷ except at age 14, where the lines coincide. The excess in stem-length of my boys over his, by calculation from the table, averages 4.4 per cent. (above Ranke's values).

Proportional Sitting-Height, Sitting-Height Index ($100 Si/H.$)—The index of sitting-height was elucidated by West.⁹ His more important inferences may be seen in the following extracts:

The curves, starting at a high per cent. at 5 years of age, drop rapidly until the twelfth year in the case of girls and the fifteenth in the case of boys. . . . These movements of the curves seem to indicate that the greater part of the growth in stature, up to the twelfth year in the case of girls and until the fifteenth year in the case of boys, is made in the lower limbs, while after these respective ages it is made in the trunk.

Girls grow more rapidly than boys up to 12 years of age, less rapidly after that age. . . . Although both sexes make greater annual rates after than before 12, yet the girls make their greatest absolute increase before, the boys theirs after that period.

These results seem conclusive evidence that women reach maturity several years before men. There seems little doubt that for all the measurements of the body, except the weight, girls have completed their growth by the eighteenth year.

Hrdlicka drew like conclusions, but expressed in terms of leg instead of in terms of trunk: "In children of small age the proportion of the length of the lower limbs to the total height of the body is comparatively small, and increases with considerable . . . regularity during all the years up to and possibly even beyond the age of puberty. This means that as a child advances in life its limbs are growing in proportion somewhat more rapidly than its body."

Hrdlicka outlined an observation and interpretation which are upheld by the present data. He wrote: "When I compare my sitting-height indexes with similar indexes obtained by Dr. West, it appears that the indexes of Dr. West's children were at all ages somewhat smaller or that the lower extremities in these children were at all ages somewhat longer than they are in our children in the asylum. . . . These figures make me think that it is possible that it is in the lower extremities where lies the principal defect in the growth of badly nourished children; but I can say nothing positive on this point."

Following this surmise by Hrdlicka, the present series of well-to-do children would be expected to display even smaller indices than was the case with West's children. Table 3 records my values, while Chart 4 demonstrates by their relation to other series that this expectation is a fact. In other words, these private schoolboys surpass public school children, and still more asylum children of the same age, not only in standing-height and in sitting-height, but also in relative length of leg; that is, they have longer legs for their height than less fortunate children.

Incidentally, it is puzzling that the curve nearest to Hrdlicka's asylum children is shown by Smedley's children, although these were

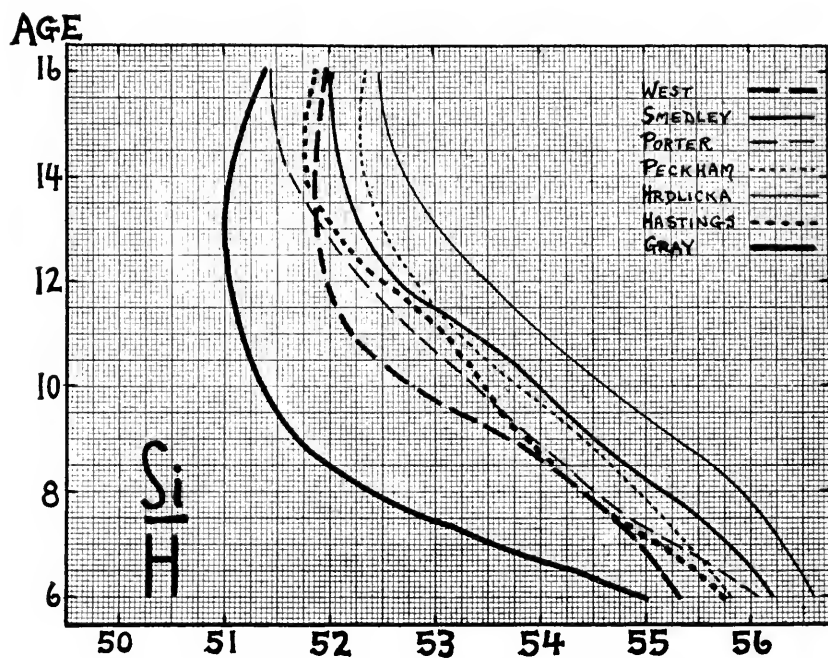


Chart 4.—Proportional sitting-height. Index: 100 Si: H.

American private schoolboys like mine, and revealed next to mine the greatest absolute sitting-heights.

Another suggestion of Hrdlicka's was that the proportions of sitting-height to total body-height can be illustrated to further advantage when we cease to consider the ages of the children and consider simply the stature. Therefore, he exposed the sitting-height index in its relation to every increase of 50 mm. in stature and from these values he drew the inference that "the relation is quite regular." However, his preferred curve as related to stature has certain irregularities that seem to me to prevent the curve from being strikingly smoother than the curve related to age; and similarly when plotted for my

children the index-curve for stature is so little smoother than the index-curve for age that the graph is not worth reproducing at present.

Theoretically, none the less, if the Si/H index should receive further study, it might well be from Hrdlicka's viewpoint, which is in keeping with the experience of several students of child physiology, as summarized elsewhere, that weight should be studied no longer in regard to age but in relation to some body measurement such as height.

Proportional Stem-Length.—A stem-length index may be examined from two angles: (1) a stem-stature index ($100\lambda/H$), and (2) a stem-sitting-height index ($100\lambda:Si$). For the new material these two series of values are condensed in Table 3, against the time when sitting-height may be supplanted by the more reliable measurement of stem-length.

TABLE 3.—INDICES OF SITTING-HEIGHT AND STEM-LENGTH (ONE HUNDRED AND FOURTEEN PRIVATE SCHOOLBOYS)

Age Nearest Birthday	Si/H	λ/H	λ/Si
6.....	54.6	53.7	98.1
7.....	54.6	53.7	98.6
8.....	52.6	52.1	99.1
9.....	51.6	51.1	98.5
10.....	51.3	51.0	99.1
11.....	51.3	50.7	98.8
12.....	50.6	49.9	98.6
13.....	51.6	50.0	97.3
14.....	50.3	48.4	96.7
15.....	51.2	49.8	97.1
16.....	51.4	49.0	96.1
17.....	50.0	49.0	97.0
18.....	50.0	49.0	97.0
Average.....	51.7	50.9	98.5

All the possible elucidations of Table 3 need not be developed here, since they are analogous to those given above for the better known measurement, sitting-height. It will suffice to note the following findings:

The average index λ/H in 114 children was 50.9, which may be compared with 51.7, the average of simultaneous observations on forty-seven healthy adult men. In ordinary speech, these children had their height distributed slightly more in the legs than was the case with the adults. This is contrary to the usual belief, as pictured in Stratz's well known diagrams,²³ that children have relatively short legs, I have no explanation to offer other than (1) accident due to the small size of both child and adult groups, or (2) that perhaps Stratz was wrong.

The mean index $\lambda:Si$ for the 114 boys was 98.5, that is, the stem-length averaged 98.5 per cent. of the sitting-height, which may be compared with 97 per cent. for adults reported by Walker.

23. Stratz, C. H.: *Darstellung des menschlichen Körpers*. Berlin, 1914.

SUMMARY

Height measurement is being rivalled and possibly superseded by measurements of the trunk independent of the legs.

The best trunk-lengths seem at present "sitting-height" and "stem-length," which are extremely similar.

These two measurements are here reported for 114 picked upper class schoolboys.

The sitting-height was not constantly parallel to the stem-length; for while it averaged half an inch greater, it varied anywhere from being identical in some boys to two inches greater in others.

The stem-length was found easier to measure accurately, i. e., with more constant agreement on repeated measurements.

The absolute values, both of stem-length and sitting-height, averaged according to age, showed greater values than any discovered in the literature. This is natural considering the advantages enjoyed by the present group of boys. In Hornor's words,²⁴ men can be bred as well as horses.

The proportional sitting-heights, or sitting-heights related to stature, or indices, were markedly less than those in the literature. This means that well-developed children have longer legs for their height than children retarded in growth; or, in Hrdlicka's words, that the principal defect of growth in badly nourished children lies in the lower extremities.

The proportional stem-lengths (indices $\lambda:H$) are also reported here but cannot be compared, as no stem-lengths for age have been detected in the literature.

It is believed that stem-length should replace sitting-height measurements in the fields of anthropology and school hygiene.

24. Hornor, A. A.: To whom I am indebted for many helpful criticisms.

THE PRESENCE OF FORMIC ACID IN THE URINE OF INFANTS AND OLDER CHILDREN *

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Formic acid has been found in the urine of normal adults by several investigators.¹ With the intention of studying its presence in the urine of children, we examined fifty-six specimens from ten infants and nine older children for a period, in most cases, of three days each. The patients were suffering from various diseases (Tables 1 and 2). The urine in all cases was negative to copper reduction tests.

The method of Autenrieth for the determination of formic acid in the urine was used. Three hundred c.c., or less, of urine, was distilled over a free flame, after the addition of 30 c.c. of 25 per cent. phosphoric acid, until about 75 c.c. remained in the flask, which was then filled to the original volume by water from a separatory funnel. The distillation was continued until the distillate was no longer acid to litmus (about 1,200 c.c. in our experiments). The distillate was then evaporated to a small volume and treated with mercuric chlorid. Formic acid, by virtue of its strong reducing power, converts mercuric chlorid to mercurous chlorid, which is filtered on a Gooch crucible and weighed. Each gram of mercurous chlorid obtained represents 0.0977 gm. formic acid. Autenrieth found that the average twenty-four hour output of formic acid by a normal adult is 0.28 gm. Another normal adult excreted 0.091 gm. in twenty-four hours. We used this method because of our inability, for several months, to secure suitable apparatus for ether

* Received for publication Dec. 29, 1921.

* The investigation was carried on in the Otho S. A. Sprague Memorial Institute Laboratory of the Children's Memorial Hospital, Chicago, and in the Section on Pediatrics of the Mayo Clinic under the direction of H. S. Amberg, Rochester, Minn.

1. Autenrieth, W.: Ueber den Ameisensäuregehalt des Harns, normalerweise und nach Eingabe verschiedener Substanzen, München. med. Wchnschr. **66**: 862, 1919.

Dakin, H. D.; Janney, N. W., and Wakeman, A. J.: Studies on the Conditions Affecting the Formation and Excretion of Formic Acid; the Estimation of Formic Acid in Urine, J. Biol. Chem. **14**:341, 1912.

Riesser, O.: Beiträge zur Frage der Ameisensäurebildung und Ausscheidung, Ztschr. f. physiol. Chem. **96**:355, 1915.

Strisower, R.: Ueber die Ausscheidung der Ameisensäure menschlichen Urine in physiologischen und pathologischen Zuständen, Biochem. Ztschr. **54**: 189, 1913.

TABLE 1.—FORMIC ACID IN THE URINE OF INFANTS

Case	Age, Mos.	Diagnosis	Date, 1920	Weight Lb. Oz.	Urine, C.c.	Sp. Gr.	Formic Acid		Diet	Stools	Remarks
							Mg.	Average for 3 Days, Mg.			
751 P. P.	4	Gastro-enteritis	9/26	8 14	270		6.67		Whole milk..... 10 oz.} 5 oz. × 4		Convalescent intoxication; received injections of glucose acacia
			9/27	8 14	285	1.004	5.02	5.11	Boiled water..... 10 oz.} 1 oz.		
			9/28	8 10	205		3.65		Dextrose maltose..... 9 oz.} 9 oz.} 4.5 oz. × 2		
751 P. P.	5	Gastro-enteritis	10/ 3	9 0	190		3.33		Alumin milk (Hoos)..... 1 oz.		Convalescent intoxication; infection originating in the ears; died 10/27/20
			10/ 4	8 14½	210	1.007	7.29	5.31	Dextrose maltose..... 1 oz.	Normal 1 to 2 daily	
			10/ 8	8 12	200	1.006	5.11	5.31	Cereal..... 1 oz.} 1 oz. × 1		
239 J. G.	5	Gastro-colitis	9/29	8 7	285	1.008	11.46		Whole milk..... 16 oz.} 5.5 oz. × 3		Moderately severe enterocolitis; improved, discharged
			9/30	8 5	265	1.008	8.59		Boiled water..... 11.5 oz.} 1 oz. × 2		
			10/ 1	8 5	125	1.011	2.71		Cereal..... 1 oz.	Normal 1 to 2 daily	
261 H. J.	6	Atrophy	10/ 6	8 4	135	1.006		7.38	Alumin milk (Hoos) 12 oz.		Marasmus; improved, discharged
			10/12	8 1½	310	1.006	13.99		Boiled water..... 9 oz.	Normal 1 in 2 to 3 days	
			10/13	8 ½	370	1.008	16.62	12.54	Dextrose maltose..... 1 oz.} 4 oz. × 6		
261 H. J.	6½	Atrophy	10/14	8 4	230	1.007	8.03		Alumin milk (Hoos)..... 1 oz.	Normal 1 daily	Probably infantilism; improved, gained well
			10/25	8 0	295	1.010	25.13		Whole milk..... 15 oz.} 4 oz. × 5		
			10/26	8 0	300	1.008	5.04		Water..... 10 oz.} 1 oz.		
235 C. L.	2	Enterocolitis	10/27	8 8	295	1.008	8.63		Farina..... 1 oz.	Loose 1 daily	Mild diarrhea; improved, discharged
			10/12	6 8	240	1.006	6.73		Dextrose maltose..... 1 oz.		
			10/13	6 8½	240	1.004	2.42	5.22	Alumin milk (Hoos) 18 oz.} 4 oz. × 6		
246 C. V.	8	Enterocolitis	10/14	6 9	375	1.005	6.31		Boiled water..... 1 oz.	Normal 1 to 2 daily	Marasmus; improved, discharged
			10/15	7 15	335	1.008	9.03		Dextrose maltose..... 1 oz.	Normal 1 to 3 daily	
			10/17	8 1½	430	1.006	7.31		Whole milk..... 10 oz.} 4.5 oz. × 6		
268 J. G.	7½	Atrophy	10/18	8 ½	280	1.007	7.60		Dextrose maltose..... 0.5 oz.	Normal constipated	Dyspepsia; improved, discharged
			10/18	7 10½	370	1.006	6.34		Whole milk..... 15 oz.} 1 oz.		
			10/19	7 13½	360	1.005	21.06	12.61	Water..... 12 oz.} 4.5 oz. × 6		
754 W. G.	8	Gastro-enteritis	10/20	7 10½	205	1.008	10.45		Farina..... 1 oz.	Loose 2 to 3 daily	Severe enteritis and meningitis; died 10/31/20
			10/25	11 7½	360	1.008	9.07		Dextrose maltose..... 1 oz.	Normal 1 to 2 daily	
			10/26	11 5	260	1.006	7.38		Whole milk..... 12 oz.} 0.5 oz. × 5		
240 R. K.	2	Enterocolitis	10/30	8 3	220	1.010	3.44		Boiled water..... 12 oz.} 4 oz. × 6		Improved, discharged
			10/31	8 3½	195	1.012	3.01	3.22	Cereal..... 0.5 oz.		
			10/19	14 0	140	1.010	7.12		Alumin milk (Hoos) 24 oz.		
188 R. B.	5	Otitis media	10/20	14 0	840	1.007	21.28	16.50	Dextrose maltose..... 1 oz.		Severe enteritis and meningitis; died 10/31/20
			10/22	14 0	190	1.010	21.20		Whole milk..... 18 oz.} 6 oz. × 5		
			10/22	14 0	190	1.010	21.20		Boiled water..... 12 oz.} 1 oz.		

TABLE 2.—FORMIC ACID IN THE URINE OF CHILDREN

Case	Age, Years	Diagnosis	Date	Weight, Pounds	Urine, C.c.	Specific Gravity	Formic Acid		Diet	Remarks
							Mg.	Average for Three Days, Mg.		
243 F. G.	7.5	Chorea	11/ 3/20 11/ 7/20 11/ 8/20	45.5	235 845 840	1.030 1.018 1.012	6.83 19.37 6.15	10.78	General, soft	Patient improved, in bed; treatment for chorea
710 A. S.	4.5	Lobar pneumonia	11/ 3/20	34	325	1.026	5.38		General	Convalescent pneumonia; patient up and about in the ward
191 L. E.	2.25	Otitis media	11/17/20 11/18/20	25	460 390	1.030 1.022	4.41 10.09	7.25	General	Up and about ward
172 T. J.	7	Cervical adenitis	11/ 8/20	50	820	1.023	19.32		General	Tonsils and adenoids removed; condition good
2844 M. B.	8	Enlarged tonsils and adenoids	11/ 9/20 11/10/20 11/11/20	47	810 790 1025	1.012 1.019 1.015	4.44 12.59 6.66	7.89	General	Chorea improved, patient in bed
245 R. P.	8.5	Chorea	11/12/20 11/13/20 11/14/20	48	970 560 840	1.014 1.018 1.012	11.95 14.81 12.7	13.15	General	Chorea improved; patient in bed
246 G. W.	9	Chorea	11/15/20 11/16/20 11/17/20	58	275 700 450	1.010 1.012 1.012	6.63 9.22 8.01	7.95	General	Chorea moderately severe; patient in bed
242 E. M.	10.75	Chorea	11/ 9/20 11/10/20 11/11/20	65	570 700 1045	1.030 1.019 1.016	22.89 31.03 39.43	31.08	General	Improved; up and about ward
245 T. H.	10.5	Chorea	11/12/21 11/13/21 11/14/21	57	750 700 830	1.020 1.020 1.020	11.82 15.62 19.39	15.61	General	Chorea improved; patient in bed

extraction of fluids. When, later, control experiments were made with the Lind apparatus, our results indicated the presence of formic acid in the urines analyzed by the former method. Dakin, Janney and Wakeman, working with the ether extraction method, found the average amount of formic acid in the urine of adults to be only 60 mg., with variations from 29.9 to 118.6 mg.

Any method involving distillation with acids is open to objection because formic acid may be derived from glucose and, perhaps, from other substances. There is no doubt that during the distillation some formic acid can arise from this source, as was shown by an increase

TABLE 3.—FORMIC ACID DETERMINATIONS

Experiment	Autenrieth Method, Mg. for Each 100 C.c.	Ether Extraction Method, Mg. for Each 100 C.c.
1.....	3.27	3.40
2.....	2.37	2.17
3.....	3.62	3.96
4.....	2.73	2.81
5.....	4.93	3.93
6.....	2.16	2.15

in the formic acid determinations of a specimen of urine from 21.7 to 106 mg. after the addition of 2 per cent. glucose. On the other hand, such a formation of formic acid apparently need not always occur, as is shown by the results obtained with parallel determinations of formic acid by the acid distillation method of Autenrieth and the ether extraction method (Table 3).

While the Autenrieth method is open to objections, the results obtained by parallel determination with the ether extraction method have been so close that we can safely conclude that the urine of children does in all likelihood contain formic acid.

THE PROPHYLACTIC AND THERAPEUTIC VALUE OF PERTUSSIS VACCINE *

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The prophylactic and therapeutic value of pertussis vaccine was demonstrated recently when an epidemic of pertussis broke out among the female inmates of the Syracuse State School for Mental Defectives. Children are 7 years of age before they are admitted to the school. The majority of the inmates are of a grade of intelligence which enables them to care for their bodily needs, but in a disease such as whooping cough, in which paroxysms occur suddenly and frequently, and are accompanied by vomiting, these mental defectives are at a disadvantage in caring for themselves.

The epidemic gained access to the institution through the agency of a little girl, who, as we discovered later, came from a territory in which the disease was prevalent at the time she was admitted to this institution. The usual procedure of placing a new admission in quarantine for two weeks was observed in this instance. The girl had a slight cold and the cough was not paroxysmal in type. She also had enlarged tonsils, and the physical findings of a mild bronchitis were elicited. She did not expectorate, vomit or whoop. At the end of two weeks she was coughing slightly, therefore quarantine was extended another week. She was a nervous child and for behavioristic reasons isolation for a longer period seemed unwarranted. She was placed in a class in the main building with thirty-one other children of about her own age. Other children in this class were coughing, but none sounded suspicious of whooping cough.

One month after our patient was released from quarantine the first whoop was reported, and in the following week several children were reported whooping, our new admission being among them.

The main building is of the old type in which the dormitories of the various classes are connected and the children housed there work and play together. It was quite probable that 177 girls had been exposed to the infection. In all, thirty-three girls were removed to the quarantine ward of the hospital with a positive diagnosis of pertussis.

The diagnosis was made in the cases which first showed symptoms of an ordinary cold and cough. In the initial stages several children had temperatures ranging as high as 100 F. There was a cough

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which became paroxysmal in type, with the physical findings of a simple bronchitis. The spasmodic character of the cough was not marked from the onset, but the whoop was noted in the majority of the cases from the beginning. The paroxysms ended with the ejection of a thick mucus and vomiting. No cultures of the expectorations were made. Smears of the expectoration in Cases 2, 7, 13 and 27 showed a gram-negative, short bacillus scattered among the pus cells. We did not attempt to examine the expectoration in all cases because of lack of time and facilities, but depended on clinical findings for a diagnosis. There were some cases which showed marked clinical evidence of pertussis in which the gram-negative, short bacillus was not found. The facies of our patients were characteristic. Swelling, congestion, injected conjunctivae, with puffy eyelids, were noted.

The New York State Department of Laboratories furnished us with sufficient vaccine to give prophylactic doses to all children who we believed had been exposed to the infection. The vaccine was dated May 2, 1921, three months before it was used (Series 39-H). On careful survey of the records and histories of the 177 girls, we found that twenty had already had the disease, 114 had not had the disease, and in forty-two cases the history and records were inadequate, so that we could not determine whether these children had had the disease. Twenty-seven of the children who developed whooping cough had not had the disease before and the remaining six were numbered among the cases in which the history and records were inadequate. In no case was there a history of a child having previously had the disease and then developing a second attack.

At the time the prophylactic vaccine injection was made we did not stop to look up past records before administering the vaccine. Three doses of vaccine were given to 143 children. The first dose was 500,000,000 units; on the third day 1,000,000,000 units were given and on the sixth day 2,000,000,000 units were injected. None of the children had severe reactions. Four of these children were sent to the quarantine ward after the first prophylactic dose was given because of the development of the paroxysmal cough with ejection of a thick mucus. Smears made from the mucus in two of these cases showed the small gram-negative bacillus among the pus cells.

The accompanying table shows the treatment and the results in the thirty-three cases in which a diagnosis of pertussis was made.

Thirteen children received five injections, one being administered every third day. The first dose was 500,000,000; the second, 1,000,000,000; the third, 3,000,000,000; the fourth, 2,000,000,000 and the fifth, 2,000,000,000. All these children persisted in coughing after the third injection; seven were coughing after the fourth injection, and six were coughing after the fifth injection. We did not give

TREATMENT AND RESULTS IN THIRTY-THREE CASES OF PERTUSSIS

Case	Diagnosis	Date of Injection	Dosage, Millions	Cough	Whooping	Vomiting	Discharge
1	Aug. 24	Aug. 24	500	+	+	+	
		Aug. 26	1,000	+	+	—	
		Aug. 29	3,000	+	+	—	
		Aug. 31	2,000	+	+	—	
		Sept. 7	2,000	—	—	—	Sept. 16
2	Aug. 24	Aug. 24	500	+	+	—	
		Aug. 26	1,000	+	+	+	
		Aug. 29	3,000	+	—	—	
		Aug. 31	2,000	—	—	—	
		Sept. 7	2,000	—	—	—	Sept. 16
3	Aug. 24	Aug. 24	500	+	+	+	
		Aug. 26	1,000	+	+	—	
		Aug. 29	3,000	+	+	—	
		Aug. 31	3,000	+	—	—	
		Sept. 7	2,000	+	—	—	
4	Aug. 24	Sept. 30	+	—	—	
		Oct. 21	—	—	—	Oct. 21
		Aug. 24	500	+	+	+	
		Aug. 26	1,000	+	+	+	
		Aug. 29	3,000	+	+	+	
5	Aug. 24	Aug. 31	2,000	+	—	—	
		Sept. 7	2,000	+	—	—	
		Oct. 7	+	—	—	Oct. 20
		Aug. 24	500	+	+	+	
		Aug. 26	1,000	+	—	+	
6	Aug. 24	Aug. 29	3,000	+	—	—	
		Aug. 31	2,000	+	—	—	
		Sept. 7	2,000	+	—	—	
		Sept. 30	+	—	—	
		Oct. 15	+	—	—	Oct. 21
7	Aug. 24	Oct. 21	—	—	—	
		Aug. 24	500	+	+	+	
		Aug. 26	1,000	+	+	+	
		Aug. 29	3,000	+	—	—	
		Aug. 31	2,000	+	—	—	
8	Aug. 24	Sept. 7	2,000	+	—	—	
		Sept. 30	+	—	—	
		Oct. 15	+	—	—	Oct. 21
		Aug. 24	500	+	—	—	
		Aug. 26	1,000	+	+	—	
9	Aug. 24	Aug. 29	3,000	+	—	—	
		Aug. 31	2,000	+	—	—	
		Sept. 7	2,000	—	—	—	Sept. 16
		Aug. 24	500	+	+	+	
		Aug. 26	1,000	+	+	—	
10	Aug. 24	Aug. 29	3,000	+	+	—	
		Aug. 31	2,000	+	+	—	
		Sept. 7	—	—	—	Sept. 16
		Aug. 24	500	+	+	+	
		Aug. 26	1,000	+	+	—	
11	Aug. 24	Aug. 29	3,000	+	—	—	
		Aug. 31	3,000	+	—	—	
		Sept. 7	2,000	—	—	—	Sept. 16
		Aug. 24	500	+	+	+	
		Aug. 26	1,000	+	—	—	
12	Aug. 24	Aug. 29	3,000	+	—	—	
		Sept. 7	2,000	—	—	—	Sept. 16
		Aug. 24	500	+	+	+	
		Aug. 26	1,000	+	—	—	
		Aug. 29	3,000	+	—	—	
13	Aug. 24	Aug. 31	2,000	—	—	—	
		Sept. 7	2,000	—	—	—	Sept. 8
		Aug. 24	500	+	+	—	
		Aug. 26	1,000	+	—	—	
		Aug. 29	3,000	+	—	—	
14	Aug. 24	Aug. 31	2,000	+	—	—	
		Sept. 7	2,000	—	—	—	Sept. 14
		Aug. 24	500	+	+	—	
		Aug. 26	1,000	+	—	—	
		Aug. 29	3,000	+	—	—	
		Aug. 31	2,000	—	—	—	
		Sept. 8	—	—	—	Sept. 8

TREATMENT AND RESULTS IN THIRTY-THREE CASES OF PERTUSSIS

Case	Diagnosis	Date of Injection	Dosage, Millions	Cough	Whooping	Vomiting	Discharge
15	Aug. 24	Aug. 24	500	+	+	—	
		Aug. 26	1,000	+	—	+	
		Aug. 29	3,000	+	—	—	
		Aug. 31	2,000	+	—	—	
		Sept. 2	—	—	—	
16	Aug. 24	Aug. 24	500	+	+	—	Sept. 8
		Aug. 26	1,000	+	+	—	
		Aug. 29	3,000	+	—	—	
		Aug. 31	2,000	+	—	—	
		Sept. 2	—	—	—	
17	Aug. 24	Aug. 24	500	+	—	—	Sept. 12
		Aug. 26	1,000	+	—	—	
		Aug. 29	3,000	+	—	—	
		Aug. 31	1,000	+	—	—	
		Sept. 18	—	—	—	
18	Aug. 24	Aug. 24	500	+	+	—	Sept. 28
		Aug. 26	1,000	+	—	—	
		Aug. 29	3,000	—	—	—	
		Aug. 31	2,000	—	—	—	
		Aug. 24	500	+	+	—	
19	Aug. 24	Aug. 24	500	+	+	—	Aug. 31
		Aug. 26	1,000	+	—	—	
		Aug. 29	3,000	+	—	—	
		Aug. 31	2,000	—	—	—	
		Aug. 24	500	+	+	—	
20	Aug. 24	Aug. 24	500	+	+	+	Aug. 31
		Aug. 26	1,000	+	—	+	
		Aug. 29	3,000	+	—	—	
		Aug. 31	2,000	+	—	—	
		Oct. 4	—	—	—	
21	Aug. 24	Aug. 24	500	+	—	—	Oct. 7
		Aug. 26	1,000	+	—	—	
		Aug. 29	3,000	+	—	—	
		Aug. 31	3,000	+	—	—	
		Sept. 7	2,000	+	—	—	
22	Aug. 24	Sept. 30	+	—	—	Oct. 21
		Oct. 15	+	—	—	
		Aug. 24	500	+	—	—	
		Aug. 26	1,000	+	—	—	
		Aug. 29	3,000	—	—	—	
23	Aug. 24	Aug. 31	2,000	—	—	—	Sept. 5
		Aug. 24	500	+	+	—	
		Aug. 26	1,000	+	+	—	
		Aug. 29	3,000*	+	+	+	
		Aug. 31	2,000	+	+	+	
24	Sept. 12	Sept. 10	—	—	—	Sept. 16
		Sept. 26	500*	+	+	+	
		Sept. 29	500*	+	+	+	
		Oct. 3	500*	+	+	+	
		Oct. 10	+	+	—	
25	Aug. 24	Oct. 15	+	—	—	
		Nov. 9	+	—	—	
		Aug. 24	500*	+	—	—	
		Aug. 29	1,000	+	—	—	
		Aug. 31	2,000	+	+	+	
26	Aug. 24	Sept. 7	2,000	+	+	—	Nov. 9
		Sept. 30	+	—	—	
		Oct. 15	+	—	—	
		Nov. 9	+	—	—	
		Aug. 24	500	+	—	—	
27	Aug. 24	Aug. 26	1,000	+	+	+	Nov. 9
		Aug. 29	3,000	+	+	+	
		Aug. 31	2,000	+	+	+	
		Sept. 7	2,000	+	+	—	
		Sept. 30	+	—	—	
28	Aug. 27	Oct. 15	+	—	—	Sept. 9
		Nov. 9	+	—	—	
		Aug. 24	500	+	—	—	
		Aug. 26	1,000	+	—	—	
		Aug. 29	3,000	+	—	—	
		Aug. 31	2,000	+	—	—	
		Sept. 1	—	—	—	
		Sept. 9	—	—	—	

TREATMENT AND RESULTS IN THIRTY-THREE CASES OF PERTUSSIS

Case	Diagnosis	Date of Injection	Dosage, Millions	Cough	Whooping	Vomiting	Discharge
29	Aug. 27	Aug. 27	2,000	+	+	—	
		Aug. 29	3,600*	+	+	—	
		Sept. 7	2,000	+	+	—	
		Sept. 30	—	—	—	
		Oct. 7	—	—	—	
30	Aug. 27	Aug. 27	500	+	+	+	Oct. 7
		Aug. 31	2,000	+	—	—	
		Sept. 7	2,000	+	—	—	
		Sept. 30	—	—	—	
		Aug. 29	500	+	—	—	
31	Aug. 29	Aug. 31	2,000	+	+	+	Oct. 4
		Sept. 7	2,000	+	+	—	
		Sept. 30	+	—	—	
		Oct. 15	—	—	—	
		Aug. 29	3,000	+	—	—	
32	Aug. 29	Aug. 31	2,000	+	—	—	Oct. 21
		Sept. 7	2,000	—	—	—	
		Sept. 11	2,000	+	+	+	
33	Sept. 11	Sept. 11	2,000	+	+	+	Sept. 16
		Sept. 26	2,000	+	+	+	
		Sept. 29	2,000	+	+	+	
		Oct. 10	—	—	—	

* Reaction.

more than five injections to any one child. Five children persisted in coughing four or five times a day for six weeks and continued to do so for ten weeks.

Before the first injection, twenty-three children were whooping; after the first injection only fourteen were whooping; after the second injection only nine were whooping; after the third injection, seven were whooping, after the fourth injection three were whooping and after the fifth injection none whooped. All whooping had ceased six weeks after the first injection was given.

Before the first injection, eleven children were vomiting, after the first injection, three were vomiting who had not vomited before and nine of the others were still vomiting; after the second injection, six were vomiting and three who had not vomited before began to vomit; after the third injection, four were vomiting; after the fourth injection, none were vomiting, and after the fifth injection none were vomiting.

Six children coughed paroxysmally when they were given their first injection. They did not develop a whoop. The cough persisted in these cases on an average of twenty-six days. The faces of these children were at first swollen and the conjunctivae were injected.

Of those children who were coughing and who had been exposed to the disease and had received their first prophylactic dose, severe coughs developed in Cases 2, 28 and 31. One child (Case 28) did not whoop or vomit but had a severe cough which developed after the first injection. A smear in this case stained by the Gram method showed a small gram-negative bacillus among the pus cells. After the patient was placed in quarantine, three additional injections were given and the clinical signs were less severe. No further smears of the mucus were made. The second child (Case 2) had a slight cough

when the first injection was given. This persisted, became decidedly paroxysmal in type and a whoop developed, with vomiting, within twenty-four hours. After the second injection there was no more whooping or vomiting, but the cough persisted until after the third injection was given. The third child (Case 31) was coughing slightly. She was given the prophylactic injection but the cough increased. The second injection was given and she developed a whoop and vomited. After the third injection the vomiting stopped, and after the fourth injection the whooping stopped. The cough persisted for a long time, not severe but bad enough to warrant keeping the child in quarantine.

Other children in the main building who had received prophylaxis did not develop the disease. Several had slight coughs but whether these were hysterical or otherwise was not ascertained at the time. After the children who were coughing and whooping were removed, and about a week after the initial prophylactic injection, the coughing in the main building practically stopped.

As to reactions from the vaccine, there were three cases. In Case 23 a reaction developed after the third injection. The child had a severe headache lasting throughout the night. There was no rise in temperature. Another child (Case 25) had a severe reaction after the first dose. Her temperature was 105.3 F. She had headache, backache and chills. The following morning the temperature was 99 F. and her condition was improved. She had no further reaction except a severe cough which lasted until November 9. This girl had a mitral regurgitation, resulting from an attack of influenza in 1918. The third child (Case 29) had a reaction after the second injection. Her temperature was 103.4 F. and she had headache and chills. Twelve hours later her condition was normal.

Case 27 was the most severe case we had. Paroxysms at first averaged eight a day. The child vomited and whooped with every paroxysm until after the fourth injection, and whooped until after the fifth injection. The cough persisted, was paroxysmal and November 9 she was coughing on an average of three times a day.

Pertussis is a disease which usually occurs in epidemic form and is contagious from person to person, but dwelling houses, school rooms and other localities may be infected by a sick child. Many persons possess immunity against the disease, but girls are more subject to it than boys. It has been pretty well proven that the Bordet-Gengou bacillus is the cause of the disease. This bacillus resembles the *Bacillus influenzae*, but it is smaller. It is a gram-negative organism and is found among the pus cells and sometimes within these cells. It stains poorly, best at the ends. It seems to be established that the greatest infectivity occurs during the initial stages of the disease, and even during the active paroxysmal stage there is less

liability of infection of others, while in the later stages there is probably no infective agent present. In the initial stage the child has symptoms of an ordinary cold with a dry bronchial cough. Mild attacks of the disease are difficult to recognize. The patient may go through the whole stages without once having a typical paroxysm and never have a whoop. In some cases of bronchitis, complicated by a laryngitis, a whoop may be present which closely resembles that of pertussis. It is these cases and the atypical cases that are difficult of diagnosis.

DISCUSSION

Pertussis gained access to the institution through a child who had been exposed to the infection before admission. The disease was unsuspected and the first case was an atypical one. Of the 176 children that had been exposed to the infection 114 had not had the disease, twenty had had the disease and the records and history were inadequate in forty-two cases. Thirty-three children developed the disease. Records in twenty-seven of these cases were negative for previous attacks and doubtful in the remaining six cases. Thirty-three children were admitted to the hospital ward with a positive diagnosis of pertussis, based in the majority of cases on the clinical findings. The remaining 143 children were given prophylactic doses of pertussis vaccine regardless of previous records or histories. After the thirty-three were removed from the main building, a diagnosis of pertussis was made in only four additional cases. We are quite sure that the majority of the children were exposed to the infection and at a time when the disease was at the stage of greatest infectivity. Most of our children are very young, and since we feel that our histories and records are quite reliable, we would say that the majority had not had pertussis. It has been stated that many persons possess an immunity against the disease and it is possible that some of the girls possessed that immunity, but girls are said to be more susceptible to the disease than boys, also it has been noted that mental defectives very readily fall prey to infections of all kinds. If the disease was in its initial stages in any of the 143 cases in which prophylactic vaccine injections were given, it was evidently checked in its development for no new cases were admitted to quarantine. If any of the cases persisted as mild or atypical cases, such as the first case was, the disease was not conveyed to any of the girls from the other buildings nor to the boys when the regular session of school opened in September and all children mingle as they do in the public schools.

Although it appears that the individual child responds differently to the pertussis vaccine, the duration of the disease is shortened by its administration. The duration in light uncomplicated cases is given

as from eight to twelve weeks; the more severe cases last a longer period. Paroxysms were lessened in severity and duration, and whooping and vomiting were alleviated.

The most severe reactions occurred in children with valvular heart lesions.

1. Osler: *Practices and Principles of Medicine*, Chicago, A. M. A. Press, 1921, p. 119-122.

2. Osborne and Fishbein: *Handbook of Therapy*, Chicago, A. M. A. Press, 1921, p. 91.

3. E. Mather Sill: *Forchheimer's Therapeutics of Internal Diseases*, Philadelphia, D. Appleton & Co. 5:300, 1916.

4. Bamberger, A.: *The Vaccine Therapy of Whooping Cough*, *Am. J. Dis. Child.* 5:21 (Jan.) 1913.

5. Hiss and Zinser: *A Textbook of Bacteriology*, New York and London, D. Appleton & Co., 1914, p. 543.

THE CHLORIN CONTENT OF COWS' AND GOATS' MILK AND FORMULAS COMMONLY USED IN INFANT FEEDING *

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Recent studies of foods emphasize the importance of their various salts to nutrition, and especially to the nutrition of growing animals. In starting an investigation of this subject in its relation to the nutrition of infants, it seemed necessary, first, to study the concentration of the various salts that are found in milk. The sodium chlorid content of human milk obtained from mothers at various stages of lactation and living under various conditions was first investigated by us.¹ It was shown that the concentration of this salt in human milk varied greatly, but that it was remarkably constant in the milk of mothers who gave relatively large amounts of milk and were able to nurse their babies satisfactorily. The present study concerns the sodium chlorid content of cows' milk, goats' milk, and formulas made from cows' milk that are commonly used in infant feeding.

The method employed for the determination of the amount of chlorin present was that of Van Slyke and Donleavy,² a slight modification of which has been described by us.¹ Five c.c. of milk was used and 10 c.c. each of picric acid and acidified silver solutions.

The specimens of whole milk examined were obtained from the Walker-Gordon dairy near Boston and from a dairy in a country district in New Hampshire. In both instances the cows were stall fed. The cows in the first dairy were giving relatively large amounts of milk and were on well established balanced rations for maximum milk production. The cows of the second dairy were giving small amounts of milk, and were fed chiefly on hay with small amounts of grain. Specimens of milk were examined from both dairies with the salt intake carefully controlled. Precautions were taken to avoid contamination from excreta. Unless otherwise stated, the specimens represent a sample of a single milking.

The materials used for the examination of cows' milk modifications were obtained from the Walker-Gordon Laboratory, the Boston Floating Hospital, the Massachusetts General Hospital and a few miscel-

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* From the Children's Medical Department and the Clinical Laboratory of the Massachusetts General Hospital.

1. Sisson, W. R., and Denis, W.: *Am. J. Dis. Child.* **21**:389 (April) 1921.

2. Van Slyke, D. D., and Donleavy, J. J.: *J. Biol. Chem.* **37**:55 (April) 1919.

laneous sources. These specimens represent types of formulas commonly used in infant feeding.

The specimens of goats' milk were obtained from three goats which had been used for experimental purposes in our laboratory. The animals were in excellent condition when the specimens were obtained, and were receiving no extra added salt in their rations.

The results of the analyses of twenty-five specimens of milk obtained from Dairy "A" (Walker-Gordon) are shown in Table 1. Most of these cows were Holsteins and gave from ten to twenty quarts of milk a day. The first twenty cows received their usual salt ration of 30 gm. a day; the last five days in the series were given 500 gm. salt twelve hours before the specimens were obtained. It will be noted that marked variations, amounting to 104.8 per cent., occurred in the chlorin content of different specimens. The average chlorin concentration of the twenty-five specimens was 108.9 mg. per hundred c.c. milk.

TABLE 1.—SHOWING CHLORIN CONTENT OF SPECIMEN OF COWS' MILK FROM DAIRY "A" *

Cow No.	Mg. Chlorin per 100 C.c. Milk	Cow No.	Mg. Chlorin per 100 C.c. Milk
1.....	78.6	14.....	130.2
2.....	105.0	15.....	77.7
3.....	73.8	16.....	131.4
4.....	137.2	17.....	100.5
5.....	112.8	18.....	92.4
6.....	124.5	19.....	91.2
7.....	111.3	20.....	108.3
8.....	111.3	21.....	122.4
9.....	108.3	22.....	104.5
10.....	95.7	23.....	103.5
11.....	103.5	24.....	156.6
12.....	88.8	25.....	102.0
13.....	151.2		

* Cows 1-20 received 30 gm. sodium chlorid daily; Cows 21-25, 500 gm. twelve hours before milking.

The chlorin concentration of specimens of twelve cows of Dairy "B" (New Hampshire dairy) is shown in Table 2. More detailed data was obtained about the cows of this herd. Their approximate weight and period of lactation are shown in Table 2. Most of these cows were Jerseys that produced a relatively small amount of milk with a high fat content. The first specimens were obtained after the cows had received no added salt in their rations for a period of five weeks. It will be noted that comparatively little variation occurred in the chlorin content of the milk of these cows, and that figures much higher than those in the previous specimens of Dairy "A" were obtained. The average chlorin concentration of specimens of this dairy was 170 mg. per hundred c.c. milk. During the twenty-four hours following the collection of the first specimens of milk from the cows of Dairy "B," 500 gm. salt were given, and other specimens were obtained. The

chlorin concentration of these is shown in Table 2, and it will be seen that essentially no change took place in the chlorin content of the milk after the addition of the salt to the rations. Further determinations were made on specimens from the same cows collected twelve hours later, and these showed almost identical results.

TABLE 2.—SHOWING CHLORIN CONTENT OF SPECIMENS OF COWS' MILK FROM DAIRY "B"

Cow No.	Age, Years	Approximate Weight, Kg.	Period of Lactation	Volume Milk Daily, C.c.	Mg. Chlorin per 100 C.c. Milk*	
					1	2
1	3	350	4 weeks	8,000	175	175
2	6	400	12 weeks	7,500	150	175
3	5	375	8 weeks	7,500	172	176
4	5	400	26 weeks	5,000	175	175
5	2	310	5 weeks	7,000	155	175
6	2	350	4 weeks	6,000	175	175
7	6	440	36 weeks	1,500	175	178
8	2	375	12 weeks	7,500	176	176
9	8	450	6 weeks	12,000	175	175
10	4	440	4 weeks	12,400	175	175
11	5	350	8 weeks	10,000	161	169
12	6	350	8 weeks	8,000	178	176

* (1) after five weeks of salt free diet; (2) after ingestion of 500 gm. sodium chlorid.

The chlorin content of specimens of milk obtained from the first and last of the milking from cows of Dairy "B" is shown in Table 3. From these analyses there is no evidence that marked variations occur in the chlorin content of the milk obtained at different periods during the day.

TABLE 3.—SHOWING CHLORIN CONTENT OF SPECIMENS FROM FIRST AND LAST OF MILKINGS FROM DAIRY "B"

Number	Mg. Chlorin per 100 C.c. Milk	
	First Milking	Last of Milking
7.....	164.1	178.8
8.....	179.4	179.4
9.....	179.1	179.1
10.....	170.7	164.1
11.....	147.3	142.5
12.....	179.4	179.1
13.....	179.4	179.4
14.....	179.4	179.4
15.....	179.1	179.1
16.....	172.2	179.4

These determinations of the chlorin content of cows' milk show that marked variations of this constituent may occur, and that differences amounting to as much as 143 per cent. are frequently found. These results are similar to those described by us¹ in the chlorin content of human milk. The variations have no relation to the salt intake or to the stage of lactation or to the time of milking. Lower chlorin concentrations occur in specimens from cows giving large amounts of milk, and conversely high concentrations of chlorin occur in specimens from cows giving a small amount of milk.

In Table 4, the chlorin content of the milk of three different goats, together with their average daily volume of milk, is shown. The chlorin concentration of these specimens ranged from 124 to 189 mg. per hundred c.c. of milk. It will be noted that higher concentrations

TABLE 4.—SHOWING CHLORIN CONTENT OF MILK FROM THREE GOATS

Goat No.	Mg. Chlorin per 100 C.c. Milk	Average 24 Hour Volume of Milk, C.c.
1.....	165	150
1.....	169	
1.....	189	
1.....	153	
1.....	148	
1.....	157	900
1.....	174	
2.....	125	
2.....	127	
2.....	128	
2.....	124	650
3.....	165	
3.....	166	
3.....	167	
3.....	156	

were found in specimens from the goat giving a small amount of milk and lower concentrations in milk from the goat giving a large amount of milk.

The results of the examination of types of various formulas for their chlorin content are shown in Table 5. More than a hundred

TABLE 5.—SHOWING CHLORIN CONTENT OF FORMULAS COMMONLY USED IN INFANT FEEDING

"A" Formula Made with Whole Milk			
Fat, per Cent.	Carbohydrate, per Cent.	Protein, per Cent.	Chlorin, Mg. per 100 C.c.
1.6	7.0	1.28	44.0
2.0	6.0	1.6	78.0
2.6	6.6	2.1	71.8
3.0	6.0	2.3	66.5
3.6	7.0	2.9	91.5
"B" Formula Made with Cream and Skimmed Milk			
1.5	7.0	1.0	35.0
2.0	6.5	...	42.0
3.0	6.0	1.0	61.8
4.0	7.0	2.0	90.0
"C" Formula Made with Cream and Whey			
1.2	6.5	90/20	144.0
1.6	5.2	80/20	141.5
2.0	6.0	90/75	112.8
2.5	7.0	90/10	137.4
2.5	6.0	90/0	151.8
"D" Miscellaneous Formulas			
Protein milk, Boston Floating Hospital.....			71.5
Protein milk, (1) powdered preparation (a).....			85.5
Protein milk, (2) powdered preparation (b).....			47.0
Protein milk, Walker-Gordon Laboratory			141.0

different mixtures were examined and findings obtained that showed considerable variation in the chlorin content, depending on the relative amount of the various ingredients used in making up the formula. Formulas made from whole milk with a percentage of fat slightly below

2 per cent. showed a chlorin concentration about that of human milk, namely from 40 to 60 mg. per hundred c.c. The amount of chlorin in the formula increased, as would be expected, when larger amounts of whole milk necessary to increase the fat content were added. Formulas that were made from cream and skimmed milk with a fat content equal to that of a formula made from whole milk, in general showed considerably lower chlorin values, and more nearly approached the chlorin content of human milk. On the other hand, formulas that were made with whey always had a very high chlorin content. These mixtures, although the percentage of fat was not higher than 2, contained more than 100 mg. chlorin per hundred c.c. of formula, and the average chlorin concentration of all these whey formulas was 150 mg.

The chlorin content of samples of "protein milk" examined showed surprising variation. In some instances the amount of chlorin was 151 mg. The preparations of dried protein milk and those made under careful laboratory supervision uniformly showed a concentration of from 47 to 85.5 mg. per hundred c.c.

It was noted that variations occurred in the chlorin concentration not only in protein milk mixtures but in all types of formulas examined, although they contained similar percentages of fat, carbohydrate and protein, and were prepared by similar methods. This fact is best explained by inaccurate methods used to estimate the organic constituents and by variations already demonstrated to exist in the chlorin content of different specimens of milk that may have been used in the different formulas.

DISCUSSION

The standards for the proper amount of "salt" in the diet of infants under normal and abnormal nutritional conditions up to the present time are largely based on clinical experience and a lack of fundamental scientific basis. Although it is recognized that sodium chlorid is an essential ingredient of the infant's diet, the exact amount for normal nutrition has not been demonstrated.

Our clinical standards for the use of "salt" in the diets of infants have been based on the fact that there is always an excess of this ingredient in the milk and that this excess was easily tolerated. It has been assumed that although the normal intake of sodium chlorid of the infant on breast milk is from 1 to 2 gm. a day, an infant may be given a cows' milk formula containing double this amount without a deleterious effect on the nutrition. Such methods are not in accord with recognized physiologic facts, and although excessive amounts of "salt" may be tolerated, as may high percentages of fat or other ingredients, nutritional disturbances may be related in some instances to their unrestricted use. Examples of the use of excessive amounts of "salt" which are associated with pathologic disturbances may be

seen after giving formulas that contain dextri-maltose with added salt. These mixtures often contain as much as 400 per cent. more sodium chlorid than human milk, and cause what must be considered pathologic gains in weight, due undoubtedly to retention of water. Similarly, disturbances associated with diarrhea are frequently noted after the use of whey mixtures which contain excessive amounts of salts. Further clinical evidence of the retention of salt to the nutritional problems of infants may be seen from the use of protein milk. This mixture contains a relatively small amount of sodium chloride and other salts, in proportion to the other organic elements, and because of this and possibly other factors, causes marked changes in nutrition with cessation of diarrhea.

SUMMARY

The studies on the sodium chlorid content of milk emphasize the marked variation of this important ingredient in different specimens of cows' and goats' milk. Furthermore, from this study and investigation by Forbes³ and by Denis and Sisson,⁴ it seems probable that these variations are not related to the salt intake in the animal's ration, but are more dependent on the species of lactating animal and on the volume of milk that is secreted. The results of the study of the salt content of various formulas indicate that, in general, excessive amounts of the ingredient are fed to infants, and that whole milk, and especially cream and skimmed milk formulas, have a salt content nearer that of human milk, while whey mixtures contain a great excess. Also it has been shown that preparations such as protein milk, which should contain a relatively small amount of salt, may contain a large amount, a fact that may explain its unfavorable action in some cases of diarrhea.

CONCLUSIONS

1. The sodium chlorid content of cows' and goats' milk varies greatly. This variation in the case of cows' milk may be 140 per cent.—in the case of goats' milk, 20 per cent.
2. The variation in the sodium chlorid concentration of cows' and goats' milk is not due to differences in the "salt" intake.
3. The sodium chlorid content of cows' and goats' milk is dependent, in part, on the volume of milk that is secreted. Animals that give a large amount of milk tend to have lower percentages of sodium chlorid, and those that give small amounts of milk have higher percentages.
4. The sodium chlorid content of formulas that are commonly used in infant feeding varies greatly, and, in general, is much in excess of that found in human milk.

3. Forbes, E. B.: *Ohio Agric. Exper. Station Bull.* 295, 1916; *ibid.* 308, 1917.

4. Denis, W., and Sisson, W. R.: *J. Biol. Chem.* 44:483 (May) 1921.

5. The sodium chlorid content of formulas made of whole milk and of cream and skimmed milk more nearly approaches that of human milk, while the chlorin content of formulas made from whey generally exceeds that found normally in human milk by 200 per cent.

6. The sodium chlorid content of "protein milk" frequently varies greatly.

CLINICAL DEPARTMENT

RESPIRATORY OBSTRUCTION RESULTING IN DEATH

CASE REPORT WITH NECROPSY FINDINGS*

JAMES W. BRUCE, M.D., AND STUART GRAVES, M.D.

LOUISVILLE, KY.

History.—J. McC, a white boy, aged 4 months, whose family history was negative, had had rhinitis two or three times. He was breast fed for three months, then he was fed on whole milk mixtures until his death. He did not have any gastro-intestinal disturbances. He was a first born child. The labor had been normal. His present illness dated from the day after his birth when his mother noticed that his breathing was more noisy than normal. He was not cyanotic and did not seem to be in distress. This noisy breathing became more and more pronounced. He had been cyanotic only once, for about five minutes, when he seemed to strangle. His appetite was good. Breathing was always more difficult after a meal or when crying.

Physical Examination.—This showed a malnourished, white, male infant, lying quietly in bed; no distress; sensorium clear; skin rather dry and hanging loosely so that it can be picked up in folds. Tissue turgor is poor. There is no enlargement of lymph nodes; no cyanosis.

Head: Anterior fontanel is of normal size, soft and pulsating; posterior fontanel is closed. Sutures are normal. Eyes: Pupils react to light; conjunctivae are pale; sclerae clear. Nasal passages are clear. Mouth: Tongue rather dry; gums and buccal mucous membrane are normal. No abnormality of the pharynx can be seen or felt. Laryngoscopic examination was not made. Ears are normal.

Chest: Well formed; not at all "barrel-shaped;" no abnormality of bony structure. Both inspiration and expiration are labored and noisy; no difference in duration of the two. On inspiration the accessory muscles of respiration are used to their full extent and the ensiform is greatly depressed. There is a loud inspiratory and expiratory stridor. This stridor is present at all times, but is much more pronounced for from one-half to one hour after feeding or when the child is crying. There is no cough.

Lungs: Percussion is normal, except over the vertebrae where dullness extends to the sixth dorsal vertebra. Breath sounds are normal, except over the area of dullness in the back, where they are harsh. No râles heard anywhere.

Heart: Normal to percussion and auscultation.

Abdomen: Soft and tympanitic throughout; no masses or tenderness. Liver is palpated 2 cm. below the costal margin in the mammary line. Spleen is not palpable. Genitalia: Normal. Extremities: Muscles wasted; little or no subcutaneous fat. Reflexes: Normal.

Roentgenograms of chest, taken at intervals of about two weeks, show no abnormality.

Pirquet Test: Twice negative. *Wassermann Test:* Negative.

Diagnosis.—Enlarged thymus.

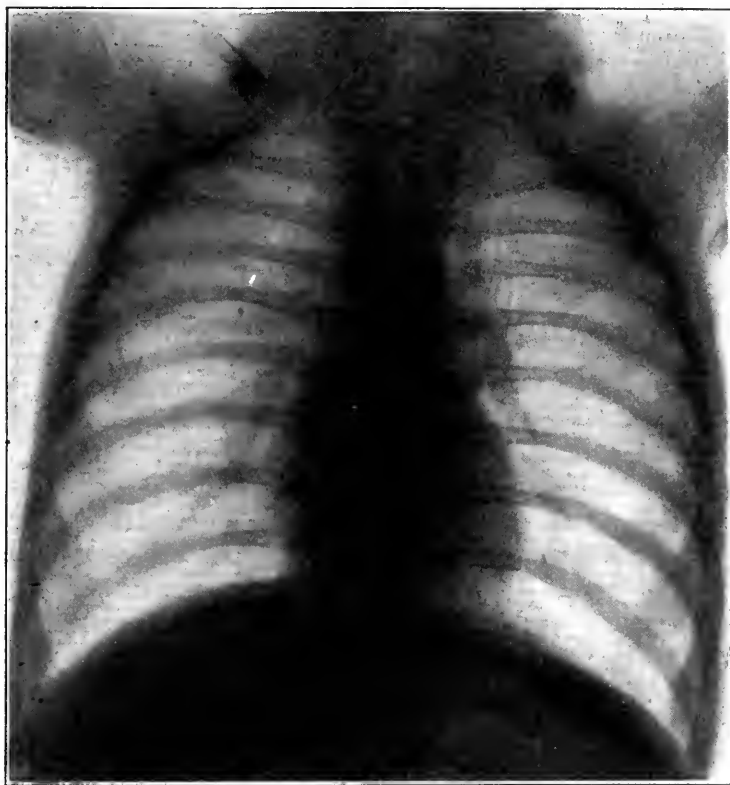
Treatment.—The baby was given roentgen-ray applications at one week intervals for four weeks. For forty-eight hours after each treatment his con-

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* From the Departments of Pediatrics and Pathology of the University of Louisville Medical School.

dition was decidedly worse, the stridor being more pronounced and the breathing more difficult, and he was slightly cyanotic. He then returned to his previous condition. He was not benefited by the roentgen-ray treatment.

The baby was fed on a 10 to 20 whole milk mixture, 5 ounces, six feedings, made up to 6 per cent. sugar with Karo corn syrup. He never had any gastrointestinal disturbance. At times he had great difficulty in swallowing his food and had to be fed with a stomach tube. The first time a stomach tube was used (No. 22 soft rubber catheter) the respirations were completely blocked and no air could pass in or out. He became cyanotic and the tube had to be withdrawn immediately. Later a smaller tube (No. 15) was used, and while it always increased the dyspnea it was possible to feed the patient in this way. The stridor was present at all times and was both inspiratory



Roentgenogram of chest with negative findings.

and expiratory. It was much worse when he was excited or after being fed, and at these times the stridor could easily be heard 75 feet away.

About one week before his death the respiratory difficulty became worse. He was now slightly cyanotic all the time. As he was more comfortable in a semirecumbent posture, he was kept propped up in this position night and day. Each feeding was an ordeal. He could not swallow the milk without aspirating some of it and having a violent coughing spell. When the small catheter was passed into his stomach, the respirations were dangerously obstructed. About forty-eight hours before his death a roentgen-ray treatment was given and shortly after this, his symptoms became greatly exaggerated and continued so until his death.

REPORT OF NECROPSY (DR. GRAVES)

Necropsy six hours after death. Body length, 63 cm. Age, 4½ months. Body is that of fairly developed, poorly nourished, white, male child. Moderate postmortem lividity in dependent portions. Rigor mortis and edema absent. Pupils equal, regular, 3 mm. in diameter. Teeth not erupted. Anterior fontanel not closed. Skin wrinkled and pale with very little subcutaneous tissue. Bones prominent and spaces sunken everywhere. Axillary glands barely palpable. The peritoneal, pericardial and pleural cavities are normal. All organs are normal. The posterior portions of the lungs are congested. The genital organs are infantile.

The thymus in situ is 50 mm. long and 35 mm. wide. Its upper portion lies 10 mm. above the sternoclavicular joint. It is roughly triangular shaped and is not remarkable except that the larger portion lies cephalic and just underneath the upper portion of the sternum in the bony inlet. Weight, 3 gm. (correct weight).

The necropsy revealed nothing remarkable except malnutrition and the unusual shape and location of the thymus. As compared with the appearance in other children examined postmortem previously and subsequently, the thymus appeared to be higher than usual and presented the larger extremity cephalad instead of caudad.

DISCUSSION

(Dr. Bruce)

The history of stridor, beginning soon after birth and continuing uninterruptedly until death, would rule out any cause which would produce spasm of the laryngeal muscles, such as spasmodic croup. These conditions are practically never seen in infants of this age.

There is a great deal in this case to suggest congenital laryngeal stridor; i. e., it was noticed soon after birth and continued unabated until the end. However, there are points which make this diagnosis impossible. In the first place, death in these cases is, so far as I know, always caused by intercurrent disease or respiratory infection, which was not present in the case under discussion. In the second place, the stridor of congenital laryngeal stridor is always inspiratory, whereas the stridor in this case was both inspiratory and expiratory and if anything expiration was a little louder than inspiration.

The postmortem appearance of the larynx was normal and there certainly was no malformation present.

From the positive D'Espine sign, I had expected to find tuberculous glands about the hilus or an enlarged thymus. There were no enlarged or tuberculous glands. The shape and position of the thymus are worthy of consideration. It was roughly diamond shaped and its greatest diameter lay in the bony thoracic inlet. The diameter of the inlet was not measured, but it takes a very small object to block it up and occlude the structures that pass through it. It seems to me that the fact that, when a No. 22 soft rubber catheter was passed through the esophagus into the stomach it completely occluded respiration, is evidence that the trouble lay in the superior thoracic inlet, as this is the only point at which the esophagus and trachea pass through an inflexible

medium. I have passed a No. 22 catheter on many other babies of the same age and never observed respiratory distress in any other case. It seems logical to believe, therefore, that even a 3 gm. thymus, if located in this narrow aperture, could cause tracheal obstruction. While it is impossible to state definitely that this was the cause of death, I think it is the most likely explanation of the case.

PROGRESS IN PEDIATRICS

A REVIEW OF THE LITERATURE OF SYPHILIS IN INFANCY AND CHILDHOOD*

PARK J. WHITE, M.D.
ST. LOUIS

Jeans¹ has reviewed the literature on this subject up to April, 1920. It is the object of the present review to bring the literature to date (December, 1921). A brief survey suffices to show the extent to which contributions from the laboratory predominate over those from clinic and practice. The reason for this is not far to seek. Syphilis, hereditary or acquired, is a disease in whose investigation and partial conquest the laboratory has played an important, an essential part. Excepting statistical reports, there are relatively few clinical observations or contributions to symptomatology. Clearly, serology, chemistry and pathology offer the widest fields for original endeavor in this disease.

INCIDENCE

Jeans and Cooke² made a study of the placentas, and of the Wassermann reactions of the cord blood of a series of 2,030 unselected infants in St. Louis. By examining the blood of 389 of these infants after 2 months of age, it was determined that the proportion of cases of hereditary syphilis that could be diagnosed with certainty by placental examination alone was 27 per cent. From the Wassermann reaction on the cord blood, 63.6 per cent. could be recognized. By applying these two methods to the series, the number of cases of hereditary syphilis in the entire group was determined to be 15 per cent. in the colored race, 1.8 per cent. in the poor of the white race, and less than 1 per cent. in the well-to-do classes. The incidence of hereditary syphilis at birth for all classes in St. Louis is 3 per cent., of which the colored population, although only 9 per cent. of the total, contributes approximately half the cases. In a somewhat similar study, Ross and Wright³ found 3.5 per cent. of the specimens of (placental) blood to be positive.

In evaluating such statistical reports, two very important factors to bear in mind are the race and the standard of living of the people.

* From the Department of Pediatrics, Washington University.

1. Jeans: *Am. J. Dis. Child.* **20**:55 and 132 (July and Aug.) 1920.

2. Jeans and Cooke: *Am. J. Dis. Child.* **22**:402 (Oct.) 1921.

3. Ross and Wright: *Lancet* **1**:321 (Feb. 12) 1921.

studied. Burhans' figure ⁴ of 1.5 per cent. (for the Babies' Dispensary and Hospital of Cleveland), is rather unusually low for clinic patients. Royster's figure ⁵ of 12.5 per cent. (for a clinic in Norfolk, Va.) is decidedly high, and may be explained by the large proportion of colored patients in the clientele. The incidence of 3 per cent. for St. Louis, and 3.5 per cent. (Ross and Wright) for an English mining and industrial town, are in fairly close agreement and are based on the entire population of each town.

RELATION OF SYPHILIS TO INFANT MORTALITY

In any consideration of deaths due to syphilis, fetal mortality assumes first place. Morgan,⁶ for example, estimates that 2,000 miscarriages and stillbirths occurred in the city of Toronto in 1920, and that 30 per cent. of these were due to syphilis—thus making 670 an index of the prenatal ravages of syphilis in that city in one year. Solomon and Solomon,⁷ in a complete study of 555 families of late syphilitics, state that 29.7 per cent. gave birth to no living children, 23 per cent. being entirely sterile, 6.7 per cent. having unsuccessful pregnancies. The 29.7 per cent. of childless syphilitics should be contrasted with 11.3 per cent. childless in a similar census group. The average birth rate per family was 2.05, and the average number of living children per family was 1.62. In the same type of population taken at random, the average birth rate per family was 3.8. How large a part syphilis plays in race suicide is thus obvious.

Williams⁸ studied 302 fetal deaths (99 white, 203 black) in 4,000 deliveries. Syphilis was responsible for 34.4 per cent. of the deaths—being the most important single cause. Allowance must, of course, be made for the fact that colored people comprised more than half the clinical material reported. The high figures for syphilis given by Williams may well be compared with those given by Meyer,⁹ who, in the course of a detailed discussion of abortion, says: "Associated constitutional or venereal diseases were recorded in only seventy-six out of 697 selected histories. In fifty-two of these, other causes for the termination of the pregnancy were also recorded." Hornung's¹⁰ figures for 221 pregnant syphilitic women in Kiel are also lower than those of Williams.

Two instructive contributions to the subject of stillbirth, giving more of its pathologic aspects, are those of F. J. Browne. In the

4. Burhans: Ohio State M. J. **17**:821 (Dec. 1) 1921.

5. Royster: Am. J. Syphilis **5**:131 (Jan.) 1921.

6. Morgan: Canad. M. A. J. **11**:849 (Nov.) 1921.

7. Solomon and Solomon: Social Hygiene **6**:469 (Oct.) 1920.

8. Williams: Bull. Johns Hopkins Hosp. **31**:141 (May) 1920.

9. Meyer: Am. J. Obst. & Gynec. **2**:138 (Aug.) 1921.

10. Hornung: Zentralbl. f. Gynäk. **44**:1222 (Oct. 23) 1920.

first¹¹ he reports a pathologic study of 200 consecutive cases of still-birth and neonatal death in the Edinburgh Royal Maternity Hospital. Twenty-two macerated fetuses are included in the series. In fourteen of these cases syphilis was the cause of fetal death. Besides the fourteen macerated fetuses there were twenty-one other cases of syphilis. Twenty-six of the total of thirty-five cases were premature. The pathologic findings reported in this and in his later articles will be discussed under pathology. Further statistics from necropsy material are those of Warwick,¹² who found 9.5 per cent. of deaths due to syphilis in 200 necropsies performed on babies who were stillborn or who died a week after birth (in the city of St. Paul).

As reports of fetal and neonatal mortality due to syphilis vary to some extent with the factors affecting each series, so do the reports of infant mortality from this cause. In the series of Solomon and Solomon,⁷ the infant mortality rate was 124 per thousand. This is less than the rate given in Massachusetts census for 1910 (i. e., 131 per thousand). Thus, in a series of children of late syphilitics, the infant mortality rate and the deaths of children under 18 do not vary greatly from the mortality as found in the community. The authors remark that the percentage of living nonsyphilitic children is considerably greater in this study than in the studies of many other investigators, due, no doubt, to unconscious selection in other studies. It is noteworthy, however, that only 30.3 per cent. of the entire group were free from defect as to children and syphilis in the spouse.

The difficulties encountered in obtaining accurate figures on infant mortality from syphilis are well described by Morgan.⁶ He found that in one year, in the city of Toronto, only nineteen certificates mentioned hereditary syphilis as a cause of death. He mentions the physicians' fear to record syphilis "to be hawked about among relatives for the delectation of prudes." This factor of concealment is no doubt often an important one. It must be borne in mind, however, as will be seen later, that often the pathologist himself is unable definitely to prove that in a given case hereditary syphilis was actually the cause of death. Athrepsia, bronchopneumonia, etc., are such frequent "terminating complications" that it is easy, though, of course, misleading, to record any of these without mentioning the underlying syphilis.

Morgan reports that of 725 successive admissions to the medical wards of the Toronto Hospital for Sick Children, twenty-nine were syphilitic—or 4 per cent. He considers that for the whole population the figure must be considerably higher. According to this writer, 90 per cent. of deaths from syphilis occur during the first year. Burhans⁴ found that the known mortality for 141 cases was forty-nine, or 34.7

11. Browne, F. J.: *Brit. M. J.* **2**:140 (July 30) 1921.

12. Warwick: *Am. J. Dis. Child.* **21**:488 (May) 1921.

per cent. In fifteen of these the cause of death was given as hereditary syphilis. Kaufmann-Wolf and Abrahamson¹³ report their fifth series of this kind. The total mortality for the five series was at least 70 per cent. when the mother was infected; and under all conditions, it was about 50 per cent. The morbidity of the living averaged 50 per cent., so that only 25 per cent. of children in the 134 families grew up healthy.

In his valuable report of the first year's work of a clinic for syphilitic children, Jewesbury¹⁴ presents the findings in 145 children whose mothers were known to be syphilitic. Of these, nine mothers became infected after the children were born—hence the disease in the children was acquired. Of the remaining 136 mothers, forty-seven had treatment during pregnancy or before. In about 50 per cent. of the cases, the disease was most marked in the early pregnancies, and apparently became gradually attenuated. But in just as many cases, children free from infection appeared in the midst of syphilitic children and miscarriages.

HEREDITARY TRANSMISSION

To gain a complete understanding of the manner of transmission of hereditary syphilis, one should study in order the "vivo and vitro" characteristics of the *Spirochaeta pallida*, its effects on the father, the mother and, through them, on their children. A sufficiently thorough consideration of all the recent literature on the spirochete would consume too much space. Some of the work done, however, requires mention—notably the experiments with rabbits by Brown and Pearce. Their results on the dissemination of spirochetes,¹⁵ the lesions of the skin,¹⁶ mucous membranes,¹⁷ eyes,¹⁸ etc., are of much value, though without immediate bearing on the transmission of syphilis to children. Their studies on latent syphilis throw some light on the important question of how a father suffering from this form of the disease may still be capable of transmitting it to his wife and thus indirectly to the offspring. Material from the popliteal nodes of six rabbits, taken after considerable period of supposed recovery, or latency, was reinoculated into other rabbits. In each case active syphilis resulted. The authors conclude that recovered rabbits may harbor virulent spirochetes almost indefinitely, even without further manifestations of activity. The lymphoid tissues of the body are probably the chief reservoirs of the virus during latent periods. Frühwald,¹⁹ reporting

13. Kaufmann-Wolf and Abrahamson: Ztschr. f. klin. Med. **89**:274, 1920.

14. Jewesbury: Lancet **1**:962 (May 7) 1921.

15. Brown and Pearce: Arch. Dermat & Syph. **2**:470 (Oct.) 1920.

16. Brown and Pearce: J. Exper. M. **32**:445 (Oct.) 1920.

17. Brown and Pearce: J. Exper. M. **32**:447 (Nov.) 1920.

18. Brown and Pearce: J. Exper. M. **34**:167 (Aug.) 1921.

19. Frühwald: Wien. klin. Wchnschr. **33**:999 (Nov. 11) 1920.

eighty-nine gland punctures in eighty-three (acquired) syphilitics, found that as the secondary stage progresses spirochetes in the glands become rarer, but that the glands may shelter them up to the third year. In four cases, latent after the conclusion of treatment, spirochetes were demonstrated in three of fourteen gland punctures.

In an experimental study of the latent syphilitic as a carrier, Eberson and Engman²⁰ isolated the spirochete from five cases out of seventy-five, ranging in latency from one to forty years after the disappearance of syphilitic signs and symptoms. Three times the organism was found in inguinal glands (in two women and one man) and twice in semen. The strains produced typical syphilitic lesions in rabbits' testicles. *Spirochaeta pallida* was isolated from patients who gave a history of syphilis dating back eleven and thirteen years, respectively, in two instances, and one year in three instances. An inguinal gland and the semen proved positive for spirochetes in the two cases first mentioned, and the glands and semen in the last named case. The blood and other body fluids, except semen, are not infectious in latent syphilis, or if so, but rarely. These facts are clearly important from the point of view of hereditary syphilis, the persistent positivity of the semen for spirochetes even after treatment or a long period of latency, indicating the difficulties in the way of protecting the prospective mother from infection by the father.

In explanation of some of the vagaries of the spirochetes, the interesting theory has been advanced that the organism passes through an intermediary or "resting" stage like that of the protozoal parasites. One of the strongest arguments in favor of the theory has been that spirochetes have never been recovered or seen during the incubation period within the rabbit's testis. According to Eberson,²¹ the absence of organisms, as judged solely by microscopic findings, is not convincing proof that a change of form has taken place within the animal body. That the *Spirochaeta pallida* is found unaltered both in morphology and in virulence in the blood and glands, seems to him sufficient to render the "resting stage" theory untenable.

If the physical obstacles to protection against infection by the husband are great, the social obstacles are still greater. Peter,²² for example, has followed 1,000 patients who had been under treatment for venereal disease at free dispensaries, and draws a gloomy picture of the heedlessness and lack of perseverance of the great majority. Roberts²³ has had the same experience. He found that severity of symptoms at

20. Eberson and Engman: J. A. M. A. **76**:160 (Jan. 15) 1921.

21. Eberson: Arch. Dermat. & Syph. **3**:111 (Feb.) 1921.

22. Peter: Schweiz. med. Wchnschr. **50**:623 (July 15) 1920; abstr. J. A. M. A. **75**:773 (Sept. 11) 1920.

23. Roberts: Lancet **2**:277 (Aug. 6) 1921.

onset had very little influence on attendance. (This factor is more important in hereditary cases in which symptoms are more likely to be alarming.) The most important factor in relation to attendance was the positivity or negativity of the Wassermann reaction. Patients (and this applies to parents, of course) must be instructed repeatedly that a negative Wassermann reaction does not mean a cure. Letter cards are an important though often unsuccessful means of getting patients to return. It is noteworthy that in Robert's series, 8.2 per cent. gave the wrong address when registering. Persons persisting in treatment until clinical and serologic cure has been effected are not protected against reinfection. Though such reinfection undoubtedly occurs, it is no evidence of curability; and these two conceptions, according to L. Jacobi,²⁴ should be dissociated.

Widakowich²⁵ gives an extensive bibliography, together with sixty-four illustrations of anomalous forms of spermatozoa in syphilitics. The percentage of pathologic forms was much higher in syphilitic than in normal men, and in heredosyphilitics than in patients with the acquired disease. Sidler-Huguenin²⁶ states that the male sexual organs are injured more than the female by inherited syphilis, judging from the smaller number of children in the families where the syphilitic is the father. He was unable to find symptoms of syphilis in the sixty-five children of the second generation, except in one doubtful case. He believes that persons with inherited syphilis can be assured that their children will not feel the effects of it, that is, of course, if they have any children, which they often do not.

Solomon and Solomon⁷ found, as they expected, a higher incidence of positive Wassermann reactions in mates than in offspring. Thirty per cent. of the spouses were positive. From 8.4 to 16.7 per cent. of the children (depending on the method of selection) were positive. Nearly one fifth of the mothers of syphilitic children gave a negative Wassermann reaction and were without symptomatic evidence of syphilis.

Riecke and Hoernicke²⁷ cite, among others, a family in which the grandfather had tabes. His daughter and her son were syphilitic. The usual difficulty of absolutely ruling out acquired syphilis in the mother was encountered. Bruusgaard²⁸ reports the fifth thoroughly studied case of hereditary syphilis in the second generation at the Christiania Hospital. The grandmother is being treated for a gummatous tertiary

24. Jacobi, L.: *Arch. Dermat. & Syph.* **2**:493, 1920.

25. Widakowich: *Semana méd.* **27**:633 (Nov. 11) 1920; abstr. *J. A. M. A.* **76**:414 (Feb. 5) 1921.

26. Sidler Huguenin: *Schweiz. med. Wchnschr.* **51**:49 (Jan. 20) 1921.

27. Riecke and Hoernicke: *München. med. Wchnschr.* **68**:1 (Jan. 7) 1921.

28. Bruusgaard: *Norsk Mag. f. Lægevidensk.* **82**:353 (May) 1921; abstr. *J. A. M. A.* **76**:1803 (June 18) 1921.

periostitis, the mother for periostitis of both tibias, and the boy, aged 8, has fan-shaped deep scars extending from the corners of the mouth. He has a two-plus Wassermann reaction. The mother during pregnancy had tertiary ulcerations and keratitis. Another family history of interest is that given by Bernheim-Carrer.²⁹ From his records, however, and from the literature in general, it would seem that definite proof of the hereditary transmission of syphilis from one generation through the two succeeding is still lacking.

The maternal, or, more accurately, the placental transmission of syphilis to offspring, is an accepted fact. Diagnosis is much more difficult in women than in men, owing to the frequent absence of symptoms. Swayne³⁰ believes that a very large number of women contract the disease innocently; and that they are more likely than men to act as innocent carriers. This author makes the general observation that syphilitic symptoms and early lesions are not so virulent now as they were many years ago; and credits the possibility that tabes and paresis are more frequent (an observation questioned by McKenna.)

Data obtained by Fischl and Steinert³¹ confirm the placental transmission of syphilis, and also, unexpectedly, confirm Profeta's law, to the extent that seventeen apparently healthy infants failed to show any sign of syphilis, although their mothers were in the most contagious phase of florid syphilis. Ten of the infants in this group never had a positive Wassermann reaction. Five of the mothers were also constantly negative, notwithstanding their florid papules at the anus, etc. Immunization by way of the placenta before birth and by suckling afterward will have to be accepted in these cases, according to the authors, even allowing for the defective production (common to the new-born) of substances yielding the Wassermann reaction. They report several infants with pronounced lesions swarming with spirochetes, but with a constantly or frequently negative Wassermann reaction. Treatment with arsphenamin did not display any provocative action in this respect. In thirty-four infants the manifestations of inherited syphilis developed late, and the Wassermann did not become positive until some time later, but in 11.7 per cent. the Wassermann veered to positive as the precursor of the clinical manifestations.

Experimental work has shown³² that the reaction of rabbits to genital inoculations of spirochetes at the time of conception differs markedly from that of normal animals. This difference extends through the period of pregnancy and well into the period of lactation. The defensive mechanism of pregnant animals is capable of opposing

29. Bernheim-Carrer: *Monatschr. f. Kinderh.* **21**:130 (May) 1921.

30. Swayne: *Brit. M. J.* **2**:476 (Sept. 24) 1921.

31. Fischl and Steinert: *Arch. f. Kinderh.* **69**:309 (June 21) 1921; abstr. *J. A. M. A.* **77**:581 (Aug. 13) 1921.

32. Brown and Pearce: *Am. J. Syphilis* **4**:593 (Oct.) 1920.

a resistance to inoculations at the time of conception, such that little or no clinical sign of infection appears.

In inherited syphilis the placenta is likely to be exceptionally large in proportion to the size of the fetus.³³ Intense local phagocytosis explains the rarity of the discovery of spirochetes in the placenta.³⁴ All of the organisms may be incorporated in phagocytes in the blood stream or in the endothelial cells of the capillaries, even when the viscera of the fetus may be swarming with spirochetes.

McWalter³⁵ reports a case to show that infection of a mother with syphilis in the eighth month of her pregnancy results in infection of the child. The syphilis in the child is of milder form, and develops later than ordinary hereditary syphilis. Gellhorn³⁶ deplores the tendency to regard maternal syphilis as unimportant, except as it affects the fetus, and contends that it is capable of producing real obstetrical complications.

THE QUESTION OF DIFFERENT STRAINS OF THE SPIROCHETE

Whether or not there are special strains of the spirochete responsible for the various clinical forms of syphilis is a question which has given rise to considerable discussion. Many of the arguments pro and con are based on hereditary transmission. Gougerot³⁷ gives an interesting review of the subject. The "pluralistes" support their contention with the fact that cases are on record of men contaminated by the same person, all having syphilis of the central nervous system. They also emphasize the occurrence of conjugal neurosyphilis; the absence of cutaneous lesions in cases of syphilis of the central nervous system; the fact that natives of the tropics seldom have syphilis of the central nervous system; the different degrees of contagiousness; "distinct evolution." The "unicistes" dispute most of these claims, and emphasize the individual differences of the various hosts.

Levaditi and Marie³⁸ give experimental evidence in favor of two types of spirochetes: the neurotropic type on the one hand, and the skin and mucous membrane type on the other. They point to the fact that rabbits inoculated with one type are not protected against the other, and that the course of the infection differs notably according to the type inoculated.

In their article on conjugal neurosyphilis, Moore and Keidel³⁹ note that the clinical evidence favoring the existence of a neurotropic strain lies partly in the comparative frequency of neurosyphilis in both

33. Lévy-Solal: *Gynéc. et Obst.* **4**:94 (Aug.) 1921.

34. Manouélian: *Gynéc. et Obst.* **3**:1 (Jan.) 1921.

35. McWalter: *Brit. M. J.* **1**:827 (June 19) 1920.

36. Gellhorn: *Surg. Gynec. & Obst.* **32**:535 (June) 1921.

37. Gougerot: *La Médecine* **2**:85 (Nov.) 1920.

38. Levaditi and Marie: *Presse méd.* **28**:646 (Sept. 15) 1920.

39. Moore and Keidel: *J. A. M. A.* **77**:1 (July 2) 1921.

partners to a marriage and in their children. They present the results of examination of forty-two wives, two mistresses, and eight husbands, being the marital partners of fifty known neurosyphilitic patients. Forty of the partners were syphilitic, and 33 per cent. of these had neurosyphilis. Though there is a high incidence of conjugal neurosyphilis in the partners of parenchymatous neurosyphilitics, the comparatively low percentage found in the partners of cerebrospinal neurosyphilitics somewhat lessens the strength of this argument for duality of strain. Feldman⁴⁰ reports a family in which the father had taboparesis with paraplegia, the mother and the oldest boy had tabes, and a younger boy had cerebrospinal syphilis with paraplegia. The first clinical symptom in each case was nystagmus. Another boy in the same family died of cerebrosyphilis. The (blood) Wassermann reaction was positive in all. The author recalls another family in which there was no neurosyphilis, though all were syphilitic. He favors the "special strain" theory, mentioning that the hereditary transmission of a poorly resisting central nervous system is hardly logical, since inherited traits cannot be transmitted from husband to wife.

Solomon and Solomon⁷ found in their series very little difference in the various percentages obtained in families of patients with general paresis and those without central nervous involvement. The problems of syphilis are practically the same from the familial point of view, whatever course the syphilis takes in the individual patient. They add that in the past numerous articles have been written to show that the offspring of paretics were remarkably healthy and quite devoid of familial syphilis. Parallel studies indicate the contrary.

Thom⁴¹ is convinced that there is no such thing as different strains in spirochetes. The selective action of spirochetes in the body is governed entirely by the manner in which the tissues of the host react. Hutinel⁴² maintains that there is one type of hereditary syphilis in which specific dystrophic changes are produced by the spirochete or its reactions, and another in which nutritional disorders are found. The endocrine glands are the tissues principally attacked. The children of such patients may also have hereditary dystrophies. Audrain⁴³ presents the tabulated details of thirty families, through three or four generations from a progenitor with unsuspected syphilis. He finds that the law of persistent localization of the lesions is confirmed, also their periodicity and the rarity of pain.

Gordon⁴⁴ cites cases of conjugal tabes and paresis from the literature, and notes reports to the effect that either partner may develop

40. Feldman: *Med. Rec.* **100**:1107 (Dec. 24) 1921.

41. Thom: *Am. J. Syphilis* **5**:9 (Jan.) 1921.

42. Hutinel, P.: *Arch. d. med. d. enf.* **23**:5, 145, 205 (Jan.-April) 1920.

43. Audrain: *Bull. Soc. de derm. et de syph.* p. 85 (Feb. 10) 1921.

44. Gordon: *Am. J. Syphilis* **5**:248 (April) 1921.

the form of neurosyphilis from which the other has been suffering, perhaps, for years. Considerable laboratory work—particularly, of course, with the cerebrospinal fluid—is required to put familial neurosyphilis on a scientific basis. Cestan, Riser, and Stillmunkés⁴⁵ have contributed to this phase of the subject in an article in which the “colloidal benzoin” reaction of the spinal fluid is discussed.

THE WASSERMANN REACTION

Since April, 1920, the literature on this subject has been abundant—one might say, lavish. The technic, or rather the technics, of the test as employed by various observers cannot be discussed here. Studies of the test as applied to syphilitic children and their families are, of course, mostly statistical. In an analysis of 4,000 Wassermann tests on pregnant women, Williams⁴⁶ found 449 positive (11.2 per cent.). Forty-three women (1 per cent.) with negative Wassermann reactions, had syphilitic children. The author believes that the evidence shows that less than half (40 per cent.) of the positive mothers will have syphilitic children. A syphilitic placenta does not inevitably mean that the child will have the disease. It will be recalled that Jeans and Cooke² found that only 27 per cent. of cases of hereditary syphilis could be diagnosed by placental examination alone, and that 63 per cent. of the cases could be recognized by the Wassermann test on the cord blood. Williams found that a positive fetal blood Wassermann was associated with a syphilitic infant in 76 per cent. of cases. His results with the Wassermann test lead him to conclude that both paternal infection of the fetus and Colles' law have neither been proved nor disproved. Having seen families in which the father has a positive Wassermann reaction and the mother a negative one, he is not as skeptical about Colles' law as are many other observers.

In a somewhat similar Wassermann study, Nobécourt and Bonnet⁴⁷ found that in pregnant women there were more positives in the seventh than in the fourth, fifth and sixth months. There was agreement between the blood of the mother and that of the baby in 90 per cent. of the cases. The majority of discrepancies were the positive—mother-negative-child reactions—which the authors attribute to postconceptional syphilis.

Goodman⁴⁸ found that in a series of 1,320 pregnant women, 87 per cent. were Wassermann negative. Of the Wassermann negative multiparas, 37 per cent. had suffered one or more miscarriages, as

45. Cestan, Riser, and Stillmunkés: *Bull. de l'Acad. de méd., Par.* **86**:116 (July 26) 1921.

46. Williams: *Bull. Johns Hopkins Hosp.* **31**:336 (Oct.) 1920.

47. Nobécourt and Bonnet: *Presse méd.* **28**:745, 1920.

48. Goodman: *Surg. Gynec. and Obst.* **30**:368, 1920.

compared with 52 per cent. of the four plus cases. Only one woman of the entire series gave a history of having been known to be infected with syphilis.

It is becoming increasingly clear that the interpretation of the Wassermann reaction, and the recording of the degree of positivity are two factors which should not be overlooked in evaluating the results of Wassermann surveys. Yet in many such surveys they are not considered. The importance of attaching proper significance to the Wassermann report is emphasized by Heagerty.⁴⁹ Quoting the All-American Conference on Venereal Diseases (December 1920): "A frank, reliable, positive Wassermann reaction should be regarded as a sign of syphilis. In the absence of all other evidences of syphilis, a diagnosis based on a positive Wassermann alone should be made with great caution, and the Wassermann report confirmed by repetition and examination in another laboratory. A negative Wassermann cannot be regarded as evidence of the absence of syphilis." Browne⁵⁰ draws practically the same conclusions.

Thaysen⁵¹ discusses the cases in which a positive Wassermann reaction does not indicate active syphilis, and analyzes active syphilis from both the clinical and biologic points of view. He declares that notwithstanding the positive Wassermann reaction in the late latent stage, the syphilis may be regarded as inactive in a large proportion of cases. His article serves to show that the terms active, inactive, and latent, are capable of various interpretations, and that such interpretations are of considerable importance to the patient from the therapeutic point of view.

The necessity for understanding the limitations of the Wassermann test is emphasized by Rohdenburg.⁵² Three important influencing factors are named: (1) The patient. Fever and other conditions, such as recent ingestion of alcohol may give a falsely positive result. Treatment should be discontinued for at least eight weeks before a negative report is accepted. (2) The collection of the specimen. (3) The technic of the test. In 148 cases with Wassermann reaction negative for three years following treatment, the reaction again became positive in five patients. (Spinal puncture was not reported in these cases.) The late quiet cases of hereditary syphilis (six in number) have never had even a temporarily negative reaction in spite of enormous dosage and long treatment. (They apparently had no examination of the spinal fluid.)

49. Heagerty: *Canad. M. A. J.* **11**:548 (Aug.) 1921.

50. Browne, F. J.: *Edinburgh M. J.* **27**:199 (Oct.) 1921.

51. Thaysen: *Ugesk. f. Laeger* **83**:759 (June 9) 1921; abstr. *J. A. M. A.* **77**:658 (Aug. 20) 1921.

52. Rohdenburg, Garbat, Spiegel and Manheims: *J. A. M. A.* **76**:14 (Jan. 1) 1921.

Discussing the various factors responsible for the positivity of the Wassermann test, Wassermann himself says⁵³ that not only protein substances, but also lipoids may produce genuine antibodies (an observation appearing more and more frequently in the literature on anaphylaxis). The syphilitic suffers from an inversion of lipid metabolism, which explains why the Wassermann reaction is positive not only with the extracts from organs of all stillborn syphilitic children, but also with all extracts containing lipid-like substances. Epstein and Paul⁵⁴ emphasize that colloidal, electric, and surface tension reactions are involved, not changes in the chemical structure of the reacting substances.

With regard to the limitations of the Wassermann reaction in hereditary syphilis, Rolleston⁵⁵ states that a positive reaction at birth is not certain evidence of syphilis, for (McIntosh and Fildes) the reacting substance may pass from mother to child in utero. The Wassermann reaction may be negative for weeks after birth, then positive. It tends to become negative about the time of puberty; and the disappearance of a positive Wassermann does not mean the absence of spirochetes. Various organs, especially the glands of internal secretion, may become involved, and the syphilis then become inactive, the symptoms being only those of involvement of such organs. If such cases are known to be syphilitic, negativity of the Wassermann does not mean that treatment is unnecessary. Quoting the work of Jeans,⁵⁶ the author adds his own experience to show the importance of testing the spinal fluid in cases of hereditary syphilis.

Cooke⁵⁷ reports 1,855 complement fixation tests for tuberculosis on 1,556 children. He makes the important observation that nonspecific fixation reactions were found in two conditions, hereditary syphilis and diphtheria. Of seventy-five hereditary syphilitics, with strongly positive Wassermann tests, twenty-one, or nearly a third, gave positive fixation tests for tuberculosis. None of the twenty-one had any demonstrable evidence of tuberculosis, though some of the older children had the usual positive Pirquet skin test. The author considers it likely that in children with a high concentration of syphilitic antibodies in the blood, the tubercle antigen has an action similar to the other non-specific lipid antigens used in the Wassermann test. The antibodies giving the Wassermann reaction are usually present in considerably higher concentration in children with hereditary syphilis than in adults with the acquired form of the disease. None of the children under one

53. Wassermann: reported in Berlin Letter, J. A. M. A. **76**:463 (Feb. 12) 1921.

54. Epstein and Paul: Med. Klin. **17**:913 (July 24) 1921; abstr. J. A. M. A. **77**:1216 (Oct. 8) 1921.

55. Rolleston, H.: Lancet **1**:471 (March 5) 1921.

56. Jeans: Am. J. Dis. Child. **18**:173, 1919.

57. Cooke: Am. J. Dis. Child. **21**:78 (Jan.) 1921.

year reacted positively to the fixation test for tuberculosis. Similarly, infants with hereditary syphilis may not develop a positive Wassermann reaction for several months. The inability to form fixing antibodies may be associated with a lack of ability to form other protective antibodies.

Another condition requiring special interpretation of the Wassermann reaction, according to Henes,⁵⁸ is hypercholesterinemia. Pregnancy, jaundice and typhoid are three of the commonest causes of increased cholesterol content of the blood. In these conditions a strongly positive reaction should be somewhat discounted, a weakly positive one given but little weight. Conversely, in chronic nephritis and in the majority of pyrexias, the cholesterol content of the blood is diminished and corresponding allowance must be made for this in reading the Wassermann test.

To investigate the not uncommon phenomenon of so-called "Wassermann-fastness," Strickler⁵⁹ endeavored to determine whether or not some of the persistently positive reactions were due to arsphenamin treatment alone. Thirty patients with various skin diseases, whose histories and physical examinations were entirely negative for syphilis, whose first Wassermann tests were negative, were given weekly injections of arsphenamin. Only eight of the completely followed group of twenty-four remained consistently negative. Nine gave a 2 plus or greater degree of positivity, five were 1 plus, two were doubtful. As none of the patients was syphilitic, these researches could not be called experiments on the provocative Wassermann reaction. In explanation of these arsenic induced reactions, the authors suggest that the arsenic in some way acts on the liver alone or on the spleen and bone marrow also; that one or all of these organs may, as a result of the arsphenamin, elaborate a lipid substance which may yield a positive Wassermann. Commenting on these observations, Kolmer⁶⁰ says that it is commonly believed that the serum of a syphilitic patient may give a negative Wassermann reaction if tested during or immediately after intravenous treatment. According to Strickler and his associates, just the reverse is to be expected. The observations of Strickler are not to be lightly dismissed, and should be held sub judice. At present Kolmer is unconvinced that arsphenamin produces such changes in nonsyphilitic individuals as would result in their serums yielding genuine positive Wassermann reactions.

A further study of Wassermann fastness is that of Stokes and Busman,⁶¹ who found that in 458 treated patients, 22 per cent. of

58. Henes: *Am. J. Syphilis* **4**:685 (Oct.) 1920.

59. Strickler, Munson and Sidlick: *J. A. M. A.* **75**:1488 (Nov. 27) 1920.

60. Kolmer: Letter to *J. A. M. A.* **75**:1796 (Dec. 25) 1920.

61. Stokes and Busman: *Am. J. M. Sc.* **110**:658 (Nov.) 1920.

latent, late and hereditary cases remained persistently Wassermann positive. They found no evidence that Wassermann fastness is the result of any special strain. Persistent positivity seems to accompany grave, rather than mild syphilis.

There is a considerable amount of recent literature on the subject of diseases other than syphilis which give a positive Wassermann reaction. Touraine⁶² names a number of tropical diseases in this class, mentioning leprosy as giving positive tests in 47 per cent. of cases—the tuberculous form even in 80 per cent.; pulmonary tuberculosis in 23.2 per cent.; lupus in 50 per cent. Prolonged ether or chloroform narcosis will give a positive Wassermann in 25 per cent. of cases. A number of blood diseases such as hemoglobulinuria, leukemia, etc., occasionally also contribute to the sources of possible error.

Recent evidence is against malaria as a cause of Wassermann positivity. Johnson⁶³ asserts that if a case is not clinically syphilitic, a positive Wassermann in any condition requires confirmation by repetition. In the various forms of malaria, the blood does not give a positive Wassermann reaction. Other causes must be operative. Iyengar⁶⁴ tested the serums of eighty-four cases of undoubted malaria in adults, and of fourteen cases in children. Seven gave a positive Wassermann. The author believes that malaria is not one of the causes of a positive reaction, and that quinin does not affect the reaction.

Studying fifty serums from patients suffering from typhus fever, Bauer⁶⁵ found that forty-six (92 per cent.) gave a positive Wassermann reaction, though none of them had any evidence of syphilis. The serums were taken during the fever period. He concludes that the Wassermann reaction is almost always positive in typhus fever when applied to inactivated serum, if the sample is taken before the crisis. He considers this of diagnostic value, since in many control cases of typhoid and paratyphoid solely negative results were secured.

Mason⁶⁶ reports two cases of diabetes mellitus, each with a strongly positive Wassermann reaction, neither having any history or symptom or sign of syphilis. Both patients were treated for their supposed syphilitic infection over a short period of time, with marked and rapid decline of their carbohydrate tolerance. The author thinks that probably the arsenic acted as a toxic agent on the weakened pancreatic cells, altering the quality or nature of their internal secretion.

It is noteworthy that Graves⁶⁷ found, in ninety controlled cases, flat discrepancies between antemortem and postmortem Wassermann reac-

62. Touraine: *Rev. de méd.* **37**:103, 1920.

63. Johnson: *J. Path. and Bacteriol.* **24**:145 (April) 1921.

64. Iyengar: *Indian J. M. Res.* **8**:136 (July) 1920.

65. Bauer: *München. med. Wchnschr.* **68**:1251 (Sept. 30) 1921.

66. Mason: *Am. J. M. Sc.* **162**:828 (Dec.) 1921.

67. Graves: *J. A. M. A.* **75**:592 (Aug. 28) 1920.

tions in only two. The postmortem Wassermann is practically as reliable as the antemortem if the serum is taken properly and if nothing unusual appears in the serum control tube.

There is persistent difference of opinion on the "provocative Wassermann reaction." Indications are that the test is losing favor. O'Leary⁶⁸ describes the method of performing the test which is used at the Mayo Clinic. Solomon and Klauder⁶⁹ found that after intravenous (or intraspinal) treatment the cerebrospinal fluid, negative before treatment, may become positive in all routine tests, or a weakly reacting fluid may become much stronger. This is compared with the Herxheimer reaction, or the production of neurorecurrences. Clinical improvement may result, and continued treatment may again produce a negative fluid.

Rusca's experience⁷⁰ with the Wassermann reaction in human milk shows that specific antibodies are present in breast milk, even in advanced lactation. The reaction is not as sensitive as that in the blood, but a positive reaction in breast milk is strong presumptive evidence in favor of grave and still active syphilis. Under specific treatment the reaction becomes negative in the milk before it disappears from the blood. Attempts at performing the Wassermann reaction on the urine have resulted unsatisfactorily on account of the frequency of anticomplementary reactions.⁷¹

FLOCCULATION REACTIONS IN SYPHILIS

In a review of this subject, Levinson⁷² gives brief descriptions of six methods of performing flocculation tests on serum. He states that none of these has been found to be specific. The Bruck silver nitrate test, already reviewed by Jeans,¹ has also been found by Levinson to be unreliable. He quotes Vernes'⁷³ opinion that in order to produce flocculation with syphilitic serums and not with normal serums, an organic colloidal preparation, rather than a mineral suspension, is necessary. He discusses the Vernes phenomenon in some detail.

The Meinicke reaction, also discussed by Levinson, is based on the hypothesis that the reaction between serum and extract takes place when extract colloids disturb the isotonicity of salt solution permitting the union of seroglobulins and lipid extract.

The Sachs-Georgi reaction⁷⁴ is a physicochemical reaction between seroglobulins and lipid extract. The globulins in syphilitic serums

68. O'Leary: *Arch. Dermat. & Syph.* **2**:348 (Sept.) 1920.

69. Solomon and Klauder: *Arch. Dermat. & Syph.* **2**:679 (Dec.) 1920.

70. Rusca: *Pediatrics* **29**:121 (Feb. 1) 1921; abstr. *J. A. M. A.* **76**:968 (April 2) 1921.

71. Klauder and Kolmer: *J. A. M. A.* **76**:102 (Jan. 8) 1921.

72. Levinson: *Am. J. Syphilis* **5**:414 (July) 1921.

73. Vernes: *Compt. rend. Acad. d. sc.* **165**: 1917; 166, 167, 1918.

74. Sachs and Georgi: Reference given by Levinson.⁷¹

are increased in amount, and the flocculate which occurs in this reaction is a lipoglobulin aggregate. It is the simplest of all flocculation reactions. Levinson compared the Wassermann, Meinicke and Sachs-Georgi reactions, using animal serums known to give positive Wassermann reactions normally. His study gives the Sachs-Georgi reaction an advantage over the Meinicke reaction. None of the flocculation reactions can at present supplant the Wassermann test. The Sachs-Georgi reaction becomes positive earlier and remains positive longer than does the Wassermann reaction.

Epstein and Paul⁷⁵ performed the "third modification" of the Meinicke test on 1,100 serums. It proved as reliable as the Wassermann test, and, the authors believe, has a number of advantages over the latter. Gloor⁷⁶ found that the Sachs-Georgi reaction agreed with the Wassermann in a higher percentage of cases than did the Meinicke reaction.

A very large number of articles have appeared giving parallel statistics of the Sachs-Georgi and Wassermann tests.⁷⁷ Parker and Haigh⁷⁸ present many such statistics of other observers, together with data of their own. They conclude that the great simplicity of the Sachs-Georgi test, and its encouraging agreement with the Wassermann, make it worthy of further study. The consensus of opinion is well summarized by Logan,⁷⁹ when he says that unless the factors which may cause the false reactions are definitely recognized and can be controlled, the test should not be used to supplant the Wassermann reaction. It may be used profitably as a control for the Wassermann.

With regard to the Sachs-Georgi reaction in the spinal fluids, Harryman⁸⁰ finds that the results closely parallel those of the Wassermann. He believes that the test is a substitute, or may be used as a valuable addition to the spinal fluid Wassermann. It furnishes a means for an earlier diagnosis of syphilis of the central nervous system than does the Wassermann. Mandelbaum⁸¹ believes that the substance responsible for the positivity of the Sachs-Georgi test is not albumin, nor globulin, but rather a member or members of the lipid group.

75. Epstein and Paul: *Med. Klin.* **17**:1118 (Sept. 11) 1921; abstr. *J. A. M. A.* **77**:1776 (Nov. 26) 1921.

76. Gloor: *Schweiz. med. Wehnschr.* **24**:466, 1920.

77. Taniguchi: *Brit. J. Exper. Path.* **2**:41 (Feb.) 1921. Taniguchi and Yoshinare: *Brit. M. J.* **2**:239 (Aug. 13) 1921. Kuner: *Wien. klin. Wehnschr.* **33**:562, 1920. Wolfstein: *Berl. klin. Wehnschr.* **56**:1110 (Nov. 24) 1919. Hull and Faught: *J. Immunol.* **5**:521 (Nov.) 1920. Messerschmidt: *Deutsch. med. Wehnschr.* **46**:150 (Feb. 5) 1920. Kilduffe: *Arch. Dermat. & Syph.* **3**:415 (April) 1921.

78. Parker and Haigh: *Arch. Dermat. & Syph.* **4**:67 (July) 1921.

79. Logan: *Lancet* **1**:14 (Jan. 1) 1921.

80. Harryman: *Arch. Dermat. & Syph.* **4**:299 (Sept.) 1921.

81. Mandelbaum: *München. med. Wehnschr.* **67**:962, 1920.

Some of the most important work on the phenomenon of serum-flocculation in the presence of colloidal solutions has been done by Vernes.⁸² He outlines the method of the "Vernes" test, in which a colloidal solution, guinea-pig serum and red cells are used, with the formation of a colorimetric scale. Marie,⁸³ reviewing the subject, says that syphilitic serum induces flocculation a little faster than normal serum—that it is merely a question of degree in a general physico-chemic phenomenon; and that Vernes' latest reaction is based on the superflaking properties of syphilitic serums as estimated with a standard opalescent scale. In Marie's opinion, it is scarcely probable that syphilis is the only disease that induces physicochemic changes in the serum; and evidence is accumulating that serum in tuberculosis and cancer may have a special action on suspensions of colloids. Cornwall and Aronson⁸⁴ believe that if confirmed the researches of Vernes will revolutionize the laboratory diagnosis of syphilis.

MISCELLANEOUS TESTS FOR SYPHILIS

The liquor formaldehydi test has not been found to be accurate. The test consists of adding a drop of ordinary liquor formaldehydi to serum without further dilution, and allowing the whole to stand for twenty-four hours at room temperature. Coagulation of the serum is a positive result. Suffern⁸⁵ believes that the test is not without value. Ecker⁸⁶ performed both the Wassermann and the formol reaction of Gates and Papacostas, in a series of 500 serums. He concluded that the formol reaction, as it stands, is of no diagnostic value because of its failure to react in clinically and serologically clear cut cases of syphilis, and because of the occurrence of positive reactions in the absence of the disease.

An interesting new serum reaction is the "sigma" reaction of Dreyer and Ward,⁸⁷ described by them as a "simple quantitative serum reaction." The authors maintain that it is more dependable than the Wassermann. The readings are expressed in terms of standard flocculation units.

Working on the speed of sedimentation of the red cells in infancy, György⁸⁸ found that in the citrated blood of infants of about 1 month, the red cells show a normal increase in the rate of sedimentation. In infants less than 1 month old, the average rate is very much slower.

82. Vernes: *Rev. neurol.* **27**:156 (Feb.) 1920.

83. Marie, P.: *Presse méd.* **28**:856 (Nov. 20) 1920; abstr. *J. A. M. A.* **76**:144 (Jan. 8) 1921.

84. Cornwall and Aronson: *J. A. M. A.* **75**:1697 (Dec. 18) 1920.

85. Suffern: *Lancet* **2**:1107 (Nov. 26) 1921.

86. Ecker: *J. Infect. Dis.* **29**:359 (Oct.) 1921.

87. Dreyer and Ward: *Lancet* **1**:956 (May 7) 1921.

88. György: *Munchen. med. Wchnschr.* **68**:808 (June 30) 1921.

In acute infections, tuberculosis, and especially in hereditary syphilis, a further marked rise in the rate of sedimentation is found. When other causes of increased rate have been ruled out, the test can be made of real service in the diagnosis of hereditary syphilis. It parallels the Wassermann and Sachs-Georgi reactions.

Starting with the known fact that inactivation of serum increases its viscosity, Holke⁸⁹ found that prolonged standing at 56 C. increases the viscosity of serums of syphilitics, treated or untreated, negative or positive, more readily than that of normal persons with negative Wassermann reactions.

With regard to the luetin test, Ward⁹⁰ found 87 per cent. of positive luetin reactions in syphilitics. In a second series of 200 cases there were 75 per cent. corroborative returns. He says that luetin as a measure of the allergic reaction in syphilis has a higher reaction both negatively and positively than has been emphasized before. Luetin itself is in need of standardization and could easily be improved.

COLLOIDAL AND OTHER REACTIONS IN THE CEREBROSPINAL FLUID

Unquestionably the colloidal gold test has successfully withstood the manifold investigations to which it has been subjected. Articles endeavoring to show that it is of value seem no longer to be necessary. Articles explaining and interpreting its action are commonly encountered. Such an article is that of Cruickshank,⁹¹ whose results confirm those of other workers. The substance in the spinal fluid of general paretics which causes the precipitation of colloidal gold is not dialyzable, and resides in the globulin fraction of the protein, and in this respect resembles the Wassermann reacting substance. It is not altered by heating to the coagulation point of protein. Syphilitic reactions are due to an amount of albumin sufficient to obscure partially the precipitating effect of the globulin. The precipitating action of paretic fluids cannot be ascribed solely to the increase in globulin, but is probably dependent on a specific alteration of the physical state of the globulin which is associated with a positive electrical charge.

Thompson⁹² presents the results of 8,400 colloidal gold tests, made on about 7,100 cerebrospinal fluids at the Massachusetts State Psychiatric Institute. Six hundred and seventy-seven gave paretic curves. The author believes that a paretic curve points toward a parenchymatous involvement of the brain, while the milder gold curves are obtained in meningitis, vascular disease, etc. The paretic curve is

89. Holke: *J. Path. & Bacteriol.* **24**:413 (Oct.) 1921.

90. Ward: *Am. J. Syphilis* **5**:482 (July) 1921.

91. Cruickshank: *Brit. J. Exper. Path.* **1**:71 (April) 1920.

92. Thompson: *Arch. Neurol. & Psychiat.* **5**:131 (Feb.) 1921.

also of considerable prognostic value. Bonsmann⁹³ found that a negative colloidal gold test could be relied on as excluding central nervous syphilis. Multiple sclerosis and brain tumors are likely to give misleading findings.

Keidel and Moore⁹⁴ state that in view of the complicated methods of preparing reagents for the colloidal gold test, the simplicity and uniformity of the colloidal mastic test (first described by Emmanuel in 1915) has much to recommend it. Both depend on colloidal phenomena. The suspension of finely divided colloidal mastic particles undergoes quantitative flocculation, as in the colloidal gold test, also culminating in complete precipitation. The authors' results on the spinal fluids of 311 patients show close parallelism between the two tests. When agreement is lacking, the mastic test seems to detect abnormalities more frequently than does the colloidal gold test. This fact, together with the simplicity of the test, lead the authors to conclude that the mastic test should be an indispensable part of spinal fluid examinations. According to Stanton,⁹⁵ the results of investigators using the mastic test have been discordant. Certain samples of gum mastic which have been found to be entirely unsuited for use in the mastic test may explain the conflicting reports.

Cestan et al.⁴⁵ note that the "colloidal benzoin" reaction often remains positive when the Wassermann has been rendered negative by treatment. This test is more likely to agree with the globulin tests than with the Wassermann and cell count.

Hektoen and Neymann⁹⁶ advance a test which they maintain is a definite index of the amount of protein in spinal fluid. Antihuman rabbit serum is added to various dilutions of the spinal fluid. In paresis they found an increase in the albumin and globulin, chiefly globulin. In epilepsy the increase is in albumin.

SYPHILIS OF THE CENTRAL NERVOUS SYSTEM

Fortunately for the proper understanding of hereditary syphilis, more work is being done on the disease as it affects the central nervous system. As in adults, almost any neurologic condition may be simulated. Tabulating the details of 114 cases of inherited neurosyphilis, Mensi⁹⁷ calls particular attention to a girl of 8 who presented the complete clinical picture of cerebrospinal sclerosis. A girl of 7 presented the spastic paralysis with a tendency to obesity, described by Marfan.

93. Bonsmann: *Deutsch. Arch. f. klin. Med.* **134**:20 (Oct. 26) 1920; abstr. *J. A. M. A.* **76**:901 (March 26) 1921.

94. Keidel and Moore: *Arch. Neurol. & Psychiat.* **6**:163 (Aug.) 1921.

95. Stanton: *Arch. Neurol. & Psychiat.* **4**:301, 1920.

96. Hektoen and Neymann: *J. A. M. A.* **75**:1332, 1920.

97. Mensi: *Riv. di clin. pediat* **19**:1 (Jan.) 1921; abstr. *J. A. M. A.* **76**:1539 (May 28) 1921.

Psychic anomalies may be due to lesions of the nervous system, or to perverted functioning of the ductless glands.

Tilton⁹⁸ reviews the literature and reports three cases of cerebro-spinal syphilis in one family. Undoubtedly, hereditary syphilis is responsible for some cases of idiocy and imbecility. Thom⁹⁹ believes that it is a most important factor. Haines and Partlow¹⁰⁰ found that of 672 children in Alabama industrial schools, 118 were feebleminded. They found no evidence of a high rate of syphilis among the mentally inferior. In a more intensive study of a smaller series, Raeder¹⁰¹ examined thirty children from 2 to 16 years old, in either or both of whose parents there was a positive Wassermann reaction (blood). "Most of the parents" had neurosyphilis, usually of the paretic type. Nineteen of the children had positive blood Wassermann reactions. Spinal puncture was done on twenty-two of the thirty children. Four of the fluids were positive. In three of these the colloidal gold curves were paretic. In the children born nearer the parental infection, not only were the physical findings and the Wassermann reactions on serum and spinal fluid positive, but these children also showed a greater degree of mental deficiency. Children born later showed less mental defect. It will be seen from the studies reported that selection of the series is an important factor in determining the extent to which inherited neurosyphilis is responsible for mental deficiency.

Virtually all workers are agreed that early examination of the spinal fluid is of paramount importance, from the point of view of therapeutics and of prognosis. It is, of course, the only means by which an asymptomatic neurosyphilis may be discovered.⁹⁹ Bigland¹⁰² says that without examination of the spinal fluid no case of organic central nervous disease should be considered syphilitic even when the blood Wassermann is positive. He also emphasizes that every case of organic central nervous disease requires spinal fluid examination even in the absence of suspected syphilis.

Kingery¹⁰³ studied the spinal fluid in fifty-two cases of hereditary syphilis. Fifteen, or 28.8 per cent. presented abnormal findings. There was a striking parallelism between the strongly positive Wassermann reactions and definite albumin and globulin increase; and an equally striking lack of parallelism between the degrees of pleocytosis and other strongly positive findings. There were four juvenile paretics and two mentally deficient cases in the series.

98. Tilton: *Northwest Med.* **20**:251 (Sept.) 1921.

99. Thom: *J. Ment. & Nerv. Dis.* **53**:8 (Jan.) 1921.

100. Haines and Partlow: *Ohio State M. J.* **16**:515 (July) 1920.

101. Raeder: *Am. J. Dis. Child.* **21**:240 (March) 1921.

102. Bigland: *Lancet* **2**:687 (Oct. 2) 1920.

103. Kingery: *J. A. M. A.* **76**:12 (Jan. 1) 1921.

In an interesting article on tuberculous meningitis and hereditary syphilis, Hutinel and Merklen¹⁰⁴ note that they have seen the two diseases associated in more than twenty cases in the past few years. They consider it proper to assume that as hereditary syphilis is an important cause of meningeal dysfunction, the implantation of tubercle bacilli as well as other germs is thereby favored. It was not until the authors began doing Wassermann tests on all cases of tuberculous meningitis that they began to realize the frequency of the association of the two conditions. (These observations should be considered in the light of Cooke's observations⁵⁷ on cross-fixation in cases of tuberculosis and of syphilis. In any event the degree of positivity of the Wassermann is of great importance in its interpretation in tuberculous patients.)

Mingazzini¹⁰⁵ reports two brothers and a sister, all of whom began to suffer at puberty from a progressive motor disturbance of the lower extremities, terminating in the syndrome of family spastic paralysis. One of the brothers also suffered from optic atrophy, choroiditis and double cataract. The father of these children was a tabetic. With the exception of the first-born (contrast with Raeder's observations¹⁰¹) all his children were more or less deficient mentally. All were syphilitic.

From five cases which Ciuffini reports,¹⁰⁶ he warns that cerebral arteritis from inherited syphilis may develop with an onset like that in the acquired disease, and the course may be the same. In eight cases, nocturnal frontal headache was the main symptom of neurosyphilis.

Parker¹⁰⁷ reviews the literature on juvenile tabes and gives a summary of seven cases. He directs attention especially to the insidious onset, lengthy and even latent course of the disease, frequency of optic atrophy, of incontinence of urine; and the relative rarity of such striking phenomena as ataxia, girdle sensations and lightning pains. There is frequently a paretic termination. The large immobile irregular pupil is more frequent with juvenile tabetic patients, in contrast to the myosis and Argyll-Robertson pupil of adult patients. Of six spinal fluid Wassermann tests, three were negative though the blood was positive. (Bigland¹⁰² would probably question the authenticity of these cases.) The observations of Rosenbeck¹⁰⁸ are in substantial agreement with those of Parker. He adds that the average age of onset of juvenile tabes is 15 years—a period equal to that between the primary lesion and tabetic manifestations in the adult. The prognosis in juvenile tabes is good for life, bad for vision.

104. Hutinel, V., and Merklen: *Arch. de méd. d. enf.* **24**:521 (Sept.) 1921.

105. Mingazzini: *Arch. Neurol. & Psychiat.* **5**:637 (June) 1921.

106. Ciuffini: *Riv. di patol. nerv.* **25**:226 (Jan.) 1921; abstr. *J. A. M. A.* **76**:1375 (May 14) 1921.

107. Parker: *Arch. Neurol. & Psychiat.* **5**:121 (Feb.) 1921.

108. Rosenbeck: *J. A. M. A.* **76**:572 (Feb. 26) 1921.

An article by Kerr,¹⁰⁹ in which he reports a case of juvenile tabes in a boy of 14, serves to illustrate how, in point of signs and laboratory findings necessary to a diagnosis of juvenile tabes, authorities differ in their criteria. The striking manifestations in Kerr's case were: (1) "painful hip," which the author believed should be interpreted as lightning pains; (2) primary optic atrophy; (3) absent knee jerks. In Kerr's opinion, these manifestations established the diagnosis of juvenile tabes in spite of the absence of a history pointing to hereditary syphilis, in spite of the negative Wassermann reaction in both blood and spinal fluid.

An important article on juvenile general paresis is that of Toni Schmidt Kräpelin.¹¹⁰ He reports thirty-nine cases of known juvenile paresis, including eight cases in which a wrong diagnosis was made, and seven cases of "preparalysis," in children who showed no clinical signs of metasyphilitic affection of the central nervous system, but in whom serologic findings characteristic of general paresis were more or less accidentally discovered. Over one fourth of the cases showed general arrest of development, one third were mentally deficient. Change in character was among the early signs. Acute onset with hemiplegia, epileptiform attacks and focal symptoms, appeared with relative frequency, suggesting a combination of epilepsy and brain syphilis. Optic atrophy without other tabetic symptoms was comparatively frequent. Total immobility of the pupil was more common than simple loss of the light reflex. In paralytic and preparalytic children, a peculiar hurried, toneless, and puffing manner of speech was noticed. Periods of excitement were common, but a persistent agitated condition was seen in only about 10 per cent. of the cases. The majority showed a typical Wassermann reaction in the blood serum and spinal fluid. No therapeutic results worth mentioning were obtained by any known treatment.

Dahlstrom¹¹¹ reports two cases of juvenile paresis, in one of which there was a misleading coincidence between trauma and the onset of the disease, with localizing neurologic signs which led to a considerable amount of brain surgery before the true condition was definitely established.

It is fortunately well-recognized that in both the acquired and hereditary forms of syphilis, infection of the central nervous system occurs early. The importance of early lumbar puncture has been urged for several years, notably by Klauder,¹¹² Fordyce,¹¹³ and in the

109. Kerr: *Lancet* **1**:598 (March 13) 1920.

110. Kräpelin, T. S.: abstr. by L. J. Pollock, *Am. J. Dis. Child.* **23**:310 (Sept.) 1920.

111. Dahlstrom: *Norsk Mag. f. Lægevidensk.* **82**:710 (Oct.) 1921.

112. Klauder: *Am. J. Syphilis* **3**:559 (Oct.) 1919.

113. Fordyce: *Am. J. M. Sc.* **161**:313 (March) 1921.

case of hereditary syphilis, by Jeans.¹¹⁴ Fordyce considers it probable that the *Spirochaeta pallida* invades the nervous system during the period of general dissemination or not at all. Wile and Hasley¹¹⁵ believe that when positive findings in the spinal fluid precede the changes in the blood, such a condition must be due to the greater delicacy of laboratory findings in the spinal fluid. Such results cannot be considered evidence for neurotropism. The authors' findings thus substantiate for the human host the observations of Brown and Pearce for dissemination in the rabbit.¹⁵

Both Bambarén¹¹⁶ and Savory¹¹⁷ urge the importance of investigating cases with epileptiform seizures for the presence of syphilis, hereditary or acquired. The former believes that the evidence is strongly against the idea of Strümpell that inherited syphilis has never been shown to be a factor in epilepsy. He cites Levy-Bing's thirteen cases of essential epilepsy, with a history of syphilis in all.

With regard to the accuracy of the blood Wassermann in neurosyphilis, Hanssen¹¹⁸ found that 13.5 per cent. of 105 patients with neurosyphilis had a negative Wassermann in the blood, but a positive one in the cerebrospinal fluid.

An experimental observation which may have some therapeutic significance is that of Weston.¹¹⁹ Working with seventeen cases of general paresis, he found that after the intraspinal injection of 1 c.c. of phenolsulphonephthalein, it took the dye from twelve to sixty-eight minutes to appear in the urine—the time in normal subjects being from four to ten minutes. As the dye was not found in fluid drawn from the cisterna magna at any time up to five hours, the author concluded that absorption in these cases took place in the lumbar region. Whether these facts might account for the practical futility of intraspinal therapy in paretics, remains to be seen.

SYPHILIS OF THE EYES

Green's first article on this subject has been reviewed by Jeans.¹ In his later publication,¹²⁰ the literature is reviewed and complete statistics given for each form of ocular disturbance encountered in the 100 cases studied by him. Particular mention should be made of the

114. Jeans: Am. J. Dis. Child. **18**:173 (Sept.) 1919.

115. Wile and Hasley: J. A. M. A. **76**:8 (Jan. 1) 1921.

116. Bambarén: Siglo méd. **68**:485 (May 21) 1921; abstr. J. A. M. A. **77**:497 (Aug. 6) 1921.

117. Savory: Lancet **2**:296 (Aug. 7) 1920.

118. Hanssen: Acta med. Scand. **53**:748 (Jan. 14) 1921; abstr. J. A. M. A. **76**:503 (March 26) 1921.

119. Weston: Arch. Neurol. & Psychiat. **5**:58 (Jan.) 1921.

120. Green: Am. J. Dis. Child. **20**:29 (July) 1920.

nineteen cases of present or past interstitial keratitis (bilateral in seventeen cases) and of the fact that fifty-two of the 100 cases presented undoubted eyeground lesions. Fourteen different types of eyeground pathology are recorded, the most characteristic being peripheral and central punctate pigmentation. Papillary haze, or "veiling" of the optic nerve head was also quite common. Occasionally the intra-ocular lesion may be the only manifestation of the hereditary syphilis.

In the course of a comparative study of syphilis in whites and negroes, Zimmermann¹²¹ has the following to say about the hereditary cases. Only the late forms of hereditary syphilis are treated in the syphilis clinic of the Johns Hopkins Hospital Dispensary where 60 per cent. of the patients are colored. No noteworthy difference between the two races with respect to late hereditary syphilis was found. Interstitial keratitis occurred in 33.3 per cent. of the white males, and in 61.7 per cent. of the white females; in 35.7 per cent. of the colored males, and in 75 per cent. of the colored females. Such predominance of keratitis in the female has been noted frequently.

Baldino¹²² reports an unusual case of bilateral congenital cataract, with marked opacity of the crystalline lens in a case of hereditary syphilis with a positive Wassermann, saddle nose and Hutchinson's teeth.

SYPHILIS OF THE AUDITORY SYSTEM

In a Wassermann survey of twenty-three deaf mutes, thirteen were found to be positive by Ardenne.¹²³ The test was positive in eight of eleven congenital cases, and in five of twelve cases in which some disease was responsible for the deafness.

Ramadier¹²⁴ gives an illustrated description of a pneumatic (Hennebert's) test of the vestibule, a positive response being nystagmus or a slow movement of the eyeballs under compression or aspiration of the air in the external ear. This "sign of a fistula without a fistula" is evidence of some lesion in the internal ear alone, and this is comparatively common with inherited syphilis. The writer never found this test positive in the normal ear, nor in other forms of ear disease. No case has yet come to necropsy, but a specific osteitis of the bony capsule of the labyrinth would explain the clinical manifestations. The test is applied with a speculum and a rubber bulb. Hennebert¹²⁵ reports three cases of deafness due to hereditary syphilis. The first

121. Zimmermann: *Arch. Dermat. & Syph.* **4**:75 (July) 1921.

122. Baldino: *Riforma med.* **36**:833 (Sept. 11) 1920.

123. Ardenne: *J. de méd. de Bordeaux* **91**:379 (July 25) 1920.

124. Ramadier: *Presse méd.* **29**:624 (Aug. 6) 1921; abstr. *J. A. M. A.* **77**:975 (Sept. 17) 1921.

125. Hennebert: *Arch. Ital. di Otol. Rhinol. e Laringol.* **31**:198, 1920; abstr. *Am. J. Syphilis* **5**:159 (Jan.) 1921.

two constitute the classical picture of hereditary syphilitic labyrinthitis. The onset of the deafness in the first case dated back to early infancy, in the second to the age of 15 years: In one of the author's cases deafness did not begin till the age of 36 years, the case being a bona fide one of hereditary syphilis. As a rule, the deafness is very pronounced. Kay¹²⁶ reports nerve deafness due to hereditary syphilis in three children in one family, their ages being 7, 5 and 4 years. In each case the evidence of the disease was manifest between the first and second years. The Wassermann was positive in the oldest child and in the parents.

TEETH

Davidsohn¹²⁷ cites the findings of Hutchinson and Neumann as to the frequency of hypoplasia of the deciduous teeth in hereditary syphilis. Such hypoplasias are also to be found in other constitutional diseases. Knowledge of their occurrence in the milk teeth of healthy, rachitic and constitutionally sick children is essential to their correct evaluation in syphilitic children. Davidsohn is convinced that true Hutchinson's teeth are pathognomonic of the disease. Though less frequent, and seldom mentioned in the literature, the enamel defects of the permanent lower central incisors may be important manifestations of hereditary syphilis. Alterations in the entire dental morphology are noted. Whether narrow, slender teeth, with large defects, are to be regarded as in the same group as Hutchinson's teeth, is not yet determined, though this conception is not without foundation. Davidsohn and Davidsohn,¹²⁸ studying fifty cases of hereditary syphilis in children more than 6 years old, found Hutchinson's teeth in twenty-four, or 48 per cent.

Sabouraud¹²⁹ says that dental stigmata often reveal otherwise unrecognized hereditary syphilis. He emphasizes the fact that certain dental buds do not develop, and that the superior lateral incisors are more likely to be lacking—or even the four lateral incisors, both upper and lower. Sometimes the cutting edge is indented. This striking deformity has been noted on one jaw in all the teeth up to the premolars. "Fish-teeth," i. e., very narrow, sharp teeth, are among the many lesions described. Enamel defects of the molars are also considered frequent. Some molars may be found with five cusps instead of four—others, which have on the internal surface the "embryo of a fifth cusp"—the so-called "tubercle of Carabelli," or mammillary eminence. Sabouraud urges that in view of the permanence and

126. Kay: J. A. M. A. **74**:1162 (April 24) 1920.

127. Davidsohn, E.: Ztschr. f. Kinderh. **25**:249, 1920.

128. Davidsohn and Davidsohn: Deutsch. med. Wchnschr. **47**:1064 (Sept. 8) 1921; abstr. J. A. M. A. **77**:1775 (Nov. 26) 1921.

129. Sabouraud: La Médecine **2**:105 (Nov.) 1920.

importance of the dental signs of hereditary syphilis, all physicians should acquaint themselves thoroughly with them.

HAIR

In an article on the relation between alopecia areata and syphilis, Sabouraud¹³⁰ states that though many cases of alopecia areata occur without demonstrable syphilitic taint, the proportion of patients with inherited syphilis is too large for a casual coincidence. His numerous experiences with the cure of alopecia areata in children under treatment for syphilis corroborate the relation between them.

CIRCULATORY SYSTEM

There has been a marked increase in the contributions to this phase of hereditary syphilis during the past year and a half. It is interesting that in 183 Wassermann tests on eighty-four children of school age with heart disease, only one test was positive.¹³¹ (Allowance must, of course, be made for the social status of the children studied, the time between the Wassermann test and parental infection, etc.) Hahn¹³² claims to have demonstrated that the majority of cases of vascular neuroses in children are referable to hereditary syphilis and to syphilitic injuries to the fetus—a claim as yet unconfirmed by other writers.

With regard to aortitis, so common in adults with the acquired disease, Stolkind¹³³ was unable to find a single instance, in the literature, of definitely proven heredosyphilitic aortitis in older children or adults, though he does not doubt the existence of such cases. He cites a case of his own with Hutchinson's teeth, positive Wassermann, etc., with aortic regurgitation and considerable cardiac involvement, which necropsy showed to be a case of serofibrinous pericarditis with verrucous endocarditis of the aortic and mitral valves. The author insists on the difficulty of excluding cardiac lesions other than syphilitic.

Calvin¹³⁴ reviews thirty-one cases of thoracic aneurysm in children, and presents two cases of his own. He thinks the evidence far from conclusive that syphilis is the sole or even the common cause of aortic aneurysm in childhood. In fact, the greater number of these cases are due to other causes, such as infectious aortitis, erosion from without, and congenital malformations. In the first of a series of studies of aneurysm, Lucke and Rea¹³⁵ state that in 247 patients, the

130. Sabouraud: *Presse méd.* **29**:581 (July 23) 1921.

131. Donaldson: *New York State J. M.* **21**:176 (May) 1921.

132. Hahn: *Zentralbl. f. inn. Med.* **42**:601 (July 30) 1921; abstr. *J. A. M. A.* **77**:1295 (Oct. 15) 1921.

133. Stolkind: *Brit. J. Child. Dis.* **17**:126 (July-Sept.) 1920.

134. Calvin: *Am. J. Dis. Child.* **21**:327 (April) 1921.

135. Lucke and Rea: *J. A. M. A.* **77**:735 (Sept. 17) 1921.

youngest was 12 days old, the oldest 91 years. More detailed pediatric data are not given in this study.

Queyrat and Mouquin¹³⁶ found signs typical of aortic stenosis in a boy of 5, whose father had congenital cataract, considered by Cantonnet to be due to hereditary syphilis. The difficulty of definite proof that such lesions are really syphilitic has been shown by the preceding articles. The same statement is true of the mitral lesions.¹³⁷ With regard to the myocardium, Friedlander¹³⁸ is of the opinion that in many instances myocardial degeneration in infancy and early childhood rests on a basis of hereditary syphilis. There is no typical form of myocarditis which might be recognized as syphilitic. In cases of heredosyphilitic myocardial degeneration, rapid improvement has followed intensive antisyphilitic treatment.

KIDNEYS

Discussing the evolution of acute nephritis in hereditary syphilitics, Queslier¹³⁹ reports finding in the literature 101 cases in which the specificity of the nephritis was established by the avowal of the parents, stigmata of the inherited disease, and positive seroreaction. Seventy-three patients were less than 2 years of age, while the remainder were of all ages up to 23 years. In all cases other prominent causes of nephritis were excluded. Only six of the seventy-three infants survived the disease, while of the twenty-nine older individuals, eighteen succumbed to the nephritis. All varieties of nephritis were found. The acute parenchymatous type was common clinically, though, strange to say, not encountered at necropsy. Naturally, renal symptoms are often masked by extensive lesions in other organs. Rolleston⁵⁵ believes that the chronic interstitial type of nephritis in early life is not so frequently due to hereditary syphilis as was formerly thought.

BONES

Gaenslen and Thalhimer¹⁴⁰ contend that our knowledge of heredosyphilitic epiphysitis is incomplete, and question the commonly accepted conception that this condition occurs only in the early months of infancy. They report a case of epiphysitis in the greater trochanter of the femur of an adolescent boy, and attribute the lesion to hereditary

136. Queyrat and Mouquin: *Bull. et mém. Soc. méd. d. hôp. de Par.* **45**:1152 (July 21) 1921.

137. Babonnei and Denoyelle: *Bull. et mém. Soc. méd. d. hôp. de Par.* **45**:774 (June 2) 1921. Amblard: *Bull. et mém. Soc. méd. d. hôp. de Par.* **45**: (May) 1921. Merklen: *Bull. et mém. Soc. méd. d. hôp. de Par.* **45**:815 (June 9) 1921.

138. Friedlander: *Gaz. d. hôp.* **93**:64 (July 20) 1920.

139. Queslier: *abstr. in Arch. Pediat.* **38**:450 (July) 1921.

140. Gaenslen and Thalhimer: *J. Orthoped. Surg.* **3**:8, 1921.

syphilis because of (1) predominance of cartilage and the riotous appearance of the process of osteogenesis; (2) lack of completion of bone formation; (3) excess of calcium deposit in the cartilage which is in apposition to the areas of bone formation; (4) the obliterating endarteritis in the thickened periosteum.

LYMPH NODES

Fabris¹⁴¹ reports the results of examination of 2,605 infants for enlargement of the epitrochlear glands. In children who presented signs of inherited syphilis, epitrochlear enlargement was evident in 32 per cent. of those under 1 year, and in 33 per cent. of those up to 2 years of age. The figures were only 7 and 9 per cent. in tuberculous children, and 7 and 11 per cent. in those with rickets. Epitrochlear adenitis, therefore, may be regarded as a confirming sign in inherited syphilis, to judge from the author's 379 cases with the inherited taint.

DYSTROPHIES AND CONGENITAL MALFORMATIONS

Hutinel and Stevenin¹⁴² name three varieties of dystrophies which are of importance in connection with hereditary syphilis: (1) the partial, local, infectious—due directly to the lesions of the disease itself—as for example the bone lesions; (2) general dystrophies, attributable to impaired function of the organs affected—particularly the endocrine glands (a theory concurred in by Barthélémy). Such cases should be treated by organotherapy as well as by antisyphilitic drugs. (3) Hereditary dystrophies due to transmission from parents to children of "organic debilities"—to the second and third generation, as for instance hyper- and hypo-thyroidism.

In the Naples children's clinic, de Stefano¹⁴³ investigated all cases with congenital anomalies. There was an overwhelming preponderance of syphilis in the antecedents of all except the cases of spina bifida.

Rios and Bisso¹⁴⁴ report a "monster from inherited syphilis." O'Brien and Mustard¹⁴⁵ quote Socin's report of a case of phocomelia with death occurring seventeen days after birth, of hereditary syphilis. A heredosyphilitic gynandroid is also reported.¹⁴⁶ Queyrat's observations on malformations of the xiphoid in hereditary syphilis are well known. Malformed spermatozoa in heredosyphilitics have already been mentioned.²⁵ Clément Simon¹⁴⁷ also reports a case with this condition.

(To be continued)

141. Fabris: *Pediatrics* **29**:193 (March 1) 1921; abstr. *J. A. M. A.* **76**:1435 (May 21) 1921.

142. Hutinel and Stevenin: *Arch. de méd. d. enf.* **23**: Nos. 1, 2, 3, 4.

143. de Stefano: *Pediatrics* **29**:59 (Jan. 15) 1921.

144. Rios and Bisso: *Semana méd.* **28**:175 (Aug. 11) 1921.

145. O'Brien and Mustard: *J. A. M. A.* **77**:1964 (Dec. 17) 1921.

146. Laiguel, Lavastine, and Boutel: *Bull. Soc. méd.* **43**:754 (May 28) 1920.

147. Simon: *Bull. Soc. franç. de dermat. et syph.* No. 6, 193, 1921.

BOOK REVIEWS

THERAPEUTISCHES VADEMEKUM FÜR DIE KINDERPRAXIS. By
PROF. HANS KLEINSCHMIDT. Berlin, S. Karger. 1920. Ed. 3. Pp. 196.

This book is a small compendium of treatment and covers very completely the conditions seen in children. The author discusses systematically general symptomatic therapy, feeding of healthy children, disturbances of nutrition, and the diseases of the new-born, of infants and of older children. Wherever possible, the question of prophylaxis is also considered. The directions are simple, clear and concise. For American readers, however, the book has the disadvantage of recommending certain proprietary remedies, which are not familiar.

UEBER KLINIK UND EPIDEMIOLOGIE DER PERTUSSIS. By Von
DR. D. POSPISCHILL. Berlin: S. Karger, 1921.

A complete and detailed account of the symptoms and treatment of whooping cough based on a large hospital experience in Vienna. After a long introduction he takes up the question of the pertussis lung. Characteristic of this are areas of bronchial breathing which change their location from day to day. This leads to many complications. In relation to tuberculosis as a complicating factor, the author states that in many thousands of necropsies on whooping cough cases, he is convinced that tuberculosis is proportionately very little influenced by whooping cough, and there are an extremely small number of florid processes in his experience. In other words, where pertussis complicates tuberculosis, the resulting death is from the pertussis and not from the tuberculosis. Also, where pertussis, measles and influenza are grouped together, the result does not seem to be materially influenced by measles, but measles seem to act as a connecting link to produce fatal results. He thinks that in large measure lung diseases in children have their origin in whooping cough, at least that has been his experience in his hospital.

He then details the various complicating lung affections of whooping cough. He discusses the effect of measles complicating whooping cough. Measles seem to act by sharpening the symptoms of whooping cough and even though several years may have elapsed between the whooping cough and the occurrence of measles, there is still evidence of the effect of the whooping cough on the lungs. Measles may lead to a recurrence of whooping cough. The effect of other infectious diseases is taken up and given in detail.

A discussion of the brain in pertussis with a detailing of the various pathologic conditions arising during the course of the disease is taken up in detail; then the vascular system, and finally pertussis pyemia, with another chapter on accidental infections occurring in pertussis. His chapter on treatment is composed largely of the prophylaxis. He believes that the best treatment for pertussis is the open air treatment winter and summer. In their hospital they have an open air pavilion in which the pertussis cases are placed.

The book is extremely detailed, perhaps too much so for a casual reader on the subject, and unfortunately, it does not possess an index, which would help one greatly in looking up a specific phase of the condition. There are a few illustrations demonstrating certain clinical features of the disease.

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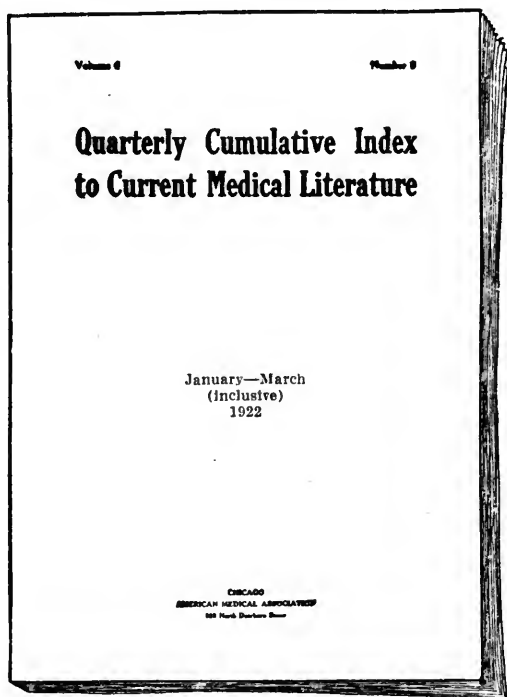
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THE FOOD REQUIREMENTS OF CHILDREN *

III. FAT REQUIREMENT

L. EMMETT HOLT, M.D., AND HELEN L. FALES

NEW YORK

The proper amount of fat which is required in the diet during growth has not been and cannot be established since the exact rôle of fat has not yet been determined. Until recently it has been generally supposed that fat did not play any specific part in nutrition, but like carbohydrate, served as a source of energy and as a sparer of protein. In fact, many observers have believed that fat and carbohydrate are practically interchangeable in the diet. Because of this belief little attention has been given to the amount of fat which is desirable in the diet, except in the case of infants. Recent investigations, however, have shown that fat is of greater importance than was formerly believed and that it has specific functions quite apart from those which it shares with the carbohydrates. It has been shown that especially during growth fat is essential. There are now admitted to be several reasons for regarding fat as an important constituent of the diet of children.

FUNCTIONS OF FAT

Fat is the purveyor of the fat soluble vitamin which has been proven to be essential for health and normal growth. A fuller discussion of this particular vitamin will be taken up later with the general subject of food accessory substances. How much of this vitamin should be provided for the child is not yet known. No one of the vitamins has as yet been isolated, consequently the chemical nature and composition of them are unknown. It is, therefore, only possible to express the vitamin content of the different foodstuffs in a relative way, that is, by comparing the value of any one food with some other used as a standard. For example, cod liver oil is used as a standard of comparison for foods containing the fat soluble vitamin A, while yeast serves as the standard for those containing the water soluble B and orange juice for those containing the antiscorbutic or vitamin C. The vitamin content of most articles of food is, however, not constant but

* Received for publication, Feb. 7, 1922.

* From the laboratories of the Rockefeller Institute for Medical Research, and the Babies' Hospital.

is influenced by a number of conditions. For example, summer milk from pastured animals has been shown to have a much higher vitamin content than winter milk from stall fed animals which received no fresh fodder.

In view of these facts it is not possible as yet to state how much fat should be given to a child in order to supply an adequate amount of fat soluble vitamin. From the evidence which has been obtained it seems quite possible that the amount of fat needed for this purpose is comparatively small. However, in order to insure normal growth, it is safer to supply generous amounts of the fats known to contain this substance. The fat soluble vitamin is most abundant in cod liver oil. Among the usual foodstuffs the richest sources are milk fats, egg yolk and certain animal organs—liver, kidneys, etc. This vitamin is also found in the leafy vegetables, but, since a child can take only a comparatively small quantity of these in the diet, it is not wise to depend on them as a source of vitamin to any great extent.

Since the function of these food accessory substances has been appreciated, there has been a growing tendency on the part of those particularly interested in them to regard the fat of the diet of special importance only as a carrier of the fat soluble vitamin. These investigators seem inclined to attribute all the bad effects of a diet low in fat to vitamin deficiency. The fact that a diet deficient in fat predisposes to rickets, that it increases the susceptibility to infection and that it retards growth is explained by them to be a result of avitaminosis. The contention is that if sufficient fat soluble vitamin is supplied in a diet which is fat free, but otherwise adequate, the conditions just mentioned will not develop.

Most of the conclusions regarding the functions of vitamins have been drawn from experiments on small laboratory animals, chiefly rats. Mendel and Osborne¹ have recently published the results of experiments in which they obtained normal growth in rats on a diet extremely low in fat, but which included the necessary amount of the fat soluble vitamin, supplied in their experiments by dried alfalfa leaves. They conclude that "if true fats are essential for nutrition during growth the minimum necessary must be exceedingly small."

To apply dogmatically to human beings the results of experiments on small animals—such as rats, which are of a species so different—seems open to question. The natural diet of the rat is very different from that of the human and consequently its digestive processes may not be entirely comparable. Hence, it is conceivable that fat may have functions in human nutrition, quite apart from that as a purveyor of vitamin A, which may not be required of it in the nutrition of the rat.

1. Osborne, T. B., and Mendel, L. B.: *J. Biol. Chem.* **45**:145 (Dec.) 1920.

Von Gröer ² has observed the effects of a diet practically fat free on two infants from birth. The food given was centrifugalized cow's milk containing only 0.01 per cent of fat with the addition of sufficient cane sugar to raise the carbohydrate content to about 8.5 per cent. of the food mixture. This diet was not only practically devoid of fat, but also extremely low in fat soluble vitamin and high in carbohydrate. Both the infants observed gained in weight with fair regularity for six months, one at the rate of 15 gm. per day and the other at the rate of 20 gm. per day. After six months the gain ceased in both. Both developed rickets and were susceptible to infection throughout the period of observation. The conclusion reached by Von Gröer is that for at least the first six months of life infants can be nourished successfully on a diet which is practically fat free, provided the calories needed are supplied by sugar. His results hardly bear out this contention.

Another function of fat which is questioned by some is its influence on mineral metabolism. This has been much debated and the subject cannot be regarded as entirely settled. Many laboratory observations have been made to ascertain the influence of the fat intake on the mineral metabolism of infants and very young children. Unfortunately, the results thus far have been contradictory and definite conclusions have not yet been reached. This is probably due to the inadequacy of the data.

Although some investigators are convinced that there is no relation between the fat intake and the mineral metabolism, we feel certain that in the case of calcium metabolism at least a very definite relation exists. The work on calcium metabolism done in this laboratory indicates that proper calcium absorption does not usually take place unless the fat in the diet bears a certain relation to the calcium and unless the intake of both is liberal. Our results indicate that the daily fat intake of children from 2 to 4 years of age should not be less than 3 gm. per kilo to insure proper absorption of calcium. This requirement seems to diminish up to 6 years of age to about 2 gm. per kilo, but is probably maintained at about this figure throughout the remainder of childhood. Since adequate absorption of calcium is necessary for bone growth, this need seems a very important one. Our results show that for the purpose of calcium absorption either animal or vegetable fat will serve equally well.

Some authors have recently taken the ground that the fat of the diet has an important influence on the metabolism of protein. Maignon ³ has discussed this question rather fully. He believes that without a proper proportion of fat in the diet the protein is not economically

2. Von Gröer, F.: *Biochem. Ztschr.* **97**:311, 1919.

3. Maignon, A.: *Ann. de méd.* **7**:280, 1920; *Compt. rend Soc. de biol.* **82**: 400, 1919.

utilized, and also that under these conditions protein forms toxic products which may be distinctly harmful. He considers that the amount of fat in the diet should not be regarded as supplementary to the dietary requirement but an integral part of it. Maignon regards as significant the fact that both in cow's milk and in woman's milk the fat exists in greater amount than the protein.

Orgler⁴ believes that, although the exact function of fat has as yet not been determined, the lack of fat certainly predisposes to edema and increases susceptibility to infection, especially to tuberculosis. This belief is quite generally accepted. Although children may apparently do well for a time on a low fat or a fat free diet, it is Orgler's opinion that a digestive upset almost inevitably follows. He considers that the complete elimination of fat from the diet or even its reduction to insignificant proportions, as proposed by Pirquet in connection with his new system of feeding, is a hazardous experiment.

It is unquestionable that a reasonable amount of fat in the diet is of service in maintaining normal conditions in the intestine. This is indicated by observations on the character and composition of stools. Stools which would be generally regarded as normal in character and consistency are not found when for a considerable time the fat of the diet has been excluded entirely or reduced to a very small amount. Only a small proportion—usually about 5 per cent.—of the ingested fat is not absorbed, but this small amount has, we believe, as Hutchison⁵ recently suggested, "a function to perform and is not a pure excretion." The fat excreted is largely in the form of soap which gives solid consistency to the stools. Again, the reaction of the stool is to a great extent dependent on the relative proportions of fat and carbohydrate in the diet. When carbohydrate forms too large a proportion of the diet, the acidity of the stool is regularly increased. When, however, there is sufficient fat in the diet to supply a normal amount of soap in the stool there is no excessive acidity. Consequently, the fat in the diet may be regarded as exerting on the mucous membrane of the intestine a protective action against the irritating effects which may be produced by fermentation of carbohydrate when this element is given in excess. This will be considered more fully in discussing carbohydrate requirement.

Aside from these reasons for regarding fat per se as an important constituent of the diet of the child, it must not be forgotten that fat as a source of energy provides more than twice as many calories per gram as does either protein or carbohydrate.

From the foregoing it seems quite clear that a considerable amount of fat is desirable and probably essential for the best nutrition of the

4. Orgler, A.: *Deutsch. med. Wchnschr.* **46**:290 (March 11) 1920.

5. Hutchison, H. S.: *Quart. J. Med.* **13**:277 (April) 1920.

growing child. The exact quantity needed, however, is difficult to determine. At the present time it can only be conjectured. Many authorities think that the diet naturally chosen is an indication of a physiologic need.

FAT IN THE DIET OF INFANTS

That fat is a natural component of the diet of the infant is shown by the composition of woman's milk. The normal amount of fat in woman's milk, on the average between 3 and 4 per cent., furnishes approximately half the total calories in the diet of the nursing infant. This cannot be without great significance. It seems hardly conceivable that so much fat would be supplied by nature if the only specific purpose of the fat were to furnish the vitamin. The nursing infant usually receives during the early weeks about 20 gm. fat daily. This increases to an average of about 40 gm. daily at the sixth or seventh month. This represents about 4 gm. per kilo of body weight.

Nature provides fat generously not only for the nursing human infant but also for the young of all mammals. The various milks all contain a considerable proportion of fat; in many of them the fat occurs in greater proportion than in woman's milk. In most milks the amount of fat and protein run almost parallel, but in several the fat considerably exceeds the protein.

The infant fed on modifications of cow's milk does not usually receive as much fat as does the nursing infant. The complete digestion of the fat of cow's milk is difficult for many infants. Consequently, it must be given in smaller amounts and increased cautiously. A widely accepted basis for the artificial feeding of the average normal infant is an allowance of 1.5 ounces of cow's milk for each pound of body weight. The fat intake calculated on this basis ranges from 15 gm. daily during the early weeks to 35 gm. daily at one year. This provides about 3.5 gm. fat per kilo of body weight. The fat allowance for different infants varies rather widely according to the individual capacity to digest cow's milk fat. Many pediatricists are inclined to attribute most of the digestive disturbances of infants to the fat of the diet and to recommend the more extensive use of skimmed milk formulas. Others consider a more liberal intake of fat to be of great advantage to most healthy children and use whole milk or in certain cases top milk of varying degrees as the basis for the milk modifications.

FAT IN THE DIET OF OLDER CHILDREN

Although there are in the literature many statements regarding the amount of fat recommended for children after infancy, there are but few actual records of the amount of fat taken in individual cases and few observations as to the effects of either a very high or a very low

fat intake. The amount of fat taken by more than one hundred normal children studied by us may, perhaps, be regarded as typical of that usually taken by healthy children.

Total Fat Daily.—The total daily amount of fat which these children received in their diet is shown in Chart I. The lines represent the grams of fat daily which would supply 35 per cent. of the total calories recommended by us in a previous paper.⁶ As will be shown later, healthy children take on the average about 35 per cent. of their total daily calories as fat. It will be seen that there is considerable variation in the individual values. However, there is a notable tendency to follow the lines indicated. Most of the instances of very high fat intake were in children of extreme activity. Two boys in their fifteenth

AVERAGE FAT INTAKE OF NORMAL CHILDREN

Age, Years	Boys			Girls			Both Sexes		
	No. of Cases	Fat Intake, Gm. Daily	Fat Intake, Gm. per Kg.	No. of Cases	Fat Intake, Gm. Daily	Fat Intake, Gm. per Kg.	No. of Cases	Fat Intake, Gm. Daily	Fat Intake, Gm. per Kg.
1-2	2	36	3.7	5	36	3.2	7	36	3.3
2-3	4	42	3.1	7	53	3.9	11	49	3.6
3-4	6	44	3.2	4	64	4.1	10	52	3.6
4-5	7	57	3.3	5	58	3.2	12	57	3.3
5-6	5	63	3.2	5	59	3.4	10	61	3.3
6-7	4	78	3.4	4	55	2.8	8	66	3.1
7-8	2	88	3.5	3	73	2.9	5	79	3.1
8-9	4	92	3.4	5	82	2.9	9	86	3.1
9-10	5	101	3.5	4	70	2.6	9	87	3.1
10-11	6	99	3.2	3	68	2.0	9	89	2.8
11-12	3	106	2.7	1	81	2.2	4	100	2.6
12-13	1	118	2.6	2	87	1.9	3	97	2.1
13-14	0	1	83	1.6	1	83	1.6
14-15	2	152	2.7	1	70	1.5	3	124	2.4
15-16	2	142	2.4	1	117	2.2	3	134	2.3
16-17	1	121	2.5	0	1	121	2.5
17-18	0	1	101	1.8	1	101	1.8

and sixteenth years, respectively, took more than 150 gm. fat daily. This large amount is indicative of the needs and habits of adolescence.

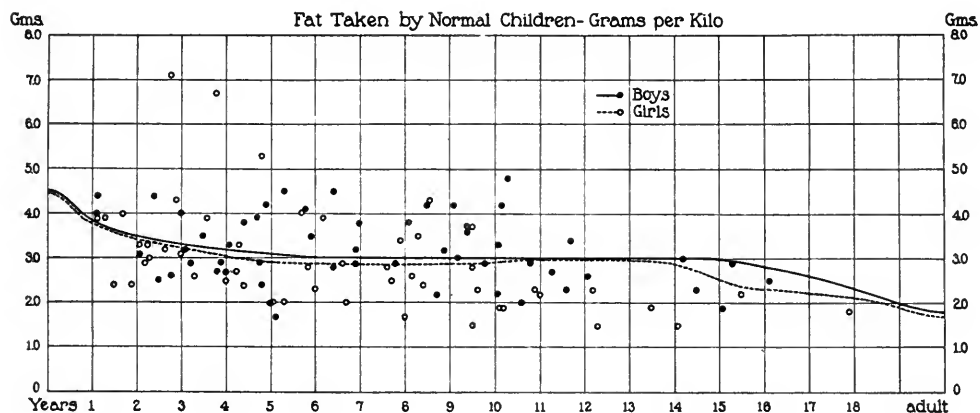
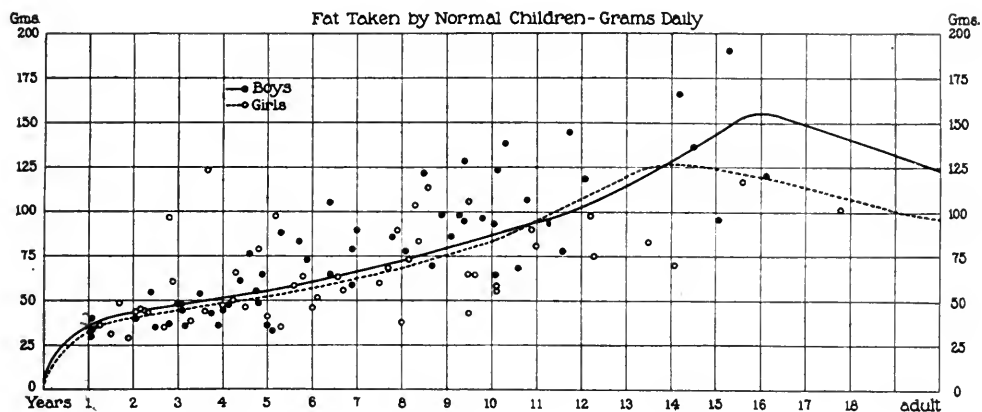
In the accompanying table are shown the average values according to years for total fat intake of the cases studied. The average values are given for boys and girls separately as well as for both sexes together. There is a practically steady increase in the average intake, reaching a maximum during the fifteenth and sixteenth years, as would be expected. The boys show a rather higher average intake than the girls.

Fat Per Kilo.—The individual values for the grams of fat per kilo taken by these children are shown in Chart 2. Although there is a considerable variation in the values, more than three-fourths of the children took between 2 and 4 gm. per kilo daily. The amounts taken by the boys show less variation than do those by the girls. The girls

6. Holt, L. E., and Fales, H. L.: Am. J. Dis. Child. **21**:1 (Jan.) 1921.

with very high intake were all healthy but extremely active children. The chart shows that as age advanced there was a gradual reduction in the grams of fat taken per kilo.

The average values for grams of fat per kilo, shown in the table, are nearly the same for both sexes during the early years—a little more than 3 gm. per kilo. Between the ages of 6 and 11 the values for the boys average a little more than 3 gm. per kilo; those for girls are



somewhat lower. After the age of 11 there are too few data to warrant conclusion.

Müller⁷ found the average fat intake of thirty-two children from 2 to 6 years of age to be 3.45 gm. per kilo, both sexes being grouped together. This value agrees with our findings for corresponding ages. Most of the other observations reported by German authors show lower values. Those of Camerer, who has been widely accepted as

7. Müller, E.: *Biochem. Ztschr.* 5:143, 1907.

an authority, are especially low, most of his values being less than 1.5 gm. per kilo. In his recommended schedule the fat allowance is only about one-half that which is usual in the diet of American children. Among the authors who have proposed a scheme of feeding in which exact quantities of the food constituents are given. Steffen⁸ is about the only one who recommends a generous fat intake. Pirquet⁹ has taken the position that fat is not a fundamentally essential article of diet and that it can be largely, if not entirely, replaced by carbohydrate without harm to the organism.

An important recent report on the amount of fat taken by older children is that found in the article by Gephart,¹⁰ who studied the diet taken by the boys of St. Paul's School, to which we have referred previously. These boys took on the average about 200 gm. fat daily. Of the three groups, the youngest, averaging 13½ years of age, took an average of 4.5 gm. fat per kilo; the middle group, averaging 14½ years, took 3.9 gm. fat per kilo; the older group, averaging 16½ years, took 3.4 gm. fat per kilo. These values are much higher than has been thought desirable for those ages. The average adult diet, based on many observations, contains only about one-half the amount of fat taken by these boys. Gephart's findings, however, are in accord with our belief that the food needs during adolescence considerably exceed those of adult life. The fact that the fat intake of so many healthy boys was so high is undoubtedly significant. This large amount of fat apparently had no deleterious effect; on the contrary, the boys thrived and it seemed to represent a physiologic need.

Certain clinicians are inclined to attribute many of the common digestive disturbances seen in older children to the fat in the diet, particularly the fat of cow's milk. It is undoubtedly true that under certain conditions a very high intake of fat, especially when accompanied by a great reduction in the carbohydrate intake, may bring about disturbances of digestion. The characteristic symptoms are coated tongue, bad breath, general malaise, constipation, with large gray stools containing a high proportion of fat, and sometimes severe and prolonged attacks of vomiting. In many such cases, however, when fat is blamed, the real cause of disturbance is too much food. This is apt to occur when children of limited activity are given more than a quart of milk, and that often rich milk, in addition to liberal amounts of solid food. It is important before lowering the fat intake to consider the diet as a whole, especially as to the total amount of food taken and the relative amounts of fat and carbohydrate which the diet contains. There is evidence that when a diet is properly balanced, that

8. Steffen, W.: *Jahrb. f. Kinderh.* **46**:332, 1898.

9. Pirquet, C.: *System der Ernährung*, Berlin, 1917.

10. Gephart, F. C.: *Boston M. & S. J.* **176**:17, 1917.

is, contains the fat, protein and carbohydrate in the right relation to each other, very much larger amounts of fat can be tolerated than when the diet is unbalanced.

Whenever the fat in the diet is much reduced it is necessary in order to supply sufficient calories to greatly increase the carbohydrate. When this is done there is always great danger of disturbing digestion from an excess of carbohydrate.

While it may not yet be established that a large amount of fat is essential in the diet during growth, there are so many reasons for a liberal allowance of fat and so little evidence that this is harmful to children with normal digestion that it does not seem wise with our present knowledge to reduce the fat much below the amount which healthy children usually take, while to exclude it entirely from the diet seems quite unjustifiable and hazardous.

SUMMARY

1. Many of the functions of fat in the diet are still subjects of debate.

2. A certain amount of fat should be supplied to provide fat soluble vitamin. This amount is not yet known. It may be exceedingly small, but until this is known it seems wise not to reduce the fat supply greatly lest there may be a deficiency in vitamin A.

3. Fat probably has an important influence on mineral metabolism, especially on calcium metabolism. For the best absorption of calcium we have found it desirable to supply as much as 3 gm. fat per kilo in the early years and as much as 2 gm. per kilo after 6 years.

4. Fat is probably necessary for proper digestion and utilization of protein and on this account it seems desirable to supply as much fat as protein in the diet.

5. Fat helps to maintain normal physical, bacteriologic and chemical conditions in the intestine. It also exerts a protective action against the irritating effects of the products of carbohydrate fermentation.

6. A great reduction of fat in the diet increases the susceptibility to infection, especially to tuberculosis.

7. The nursing infant receives a generous amount of fat, usually as much as 4 gm. per kilo daily.

8. The infant taking modifications of cow's milk usually receives about 3.5 gm. fat per kilo daily.

9. Older children studied by us took on the average over 3 gm. fat per kilo daily when under 6 years of age and about 3 gm. per kilo during the remainder of the growth period.

10. The grounds for the current impression regarding the harmful effects of fat on children should be investigated carefully. There is little evidence that a liberal amount of fat in the diet is harmful to

children with normal digestion and much evidence that fat is an important and necessary component of the diet during the entire growth period.

11. In general, it seems rational to supply in the diet of the child as much as 4 gm. fat per kilo daily at one year, decreasing the amount to about 3 gm. per kilo at 6 years and maintaining this value throughout the remainder of the growth period.

THE FREQUENCY OF TUBERCULOSIS IN CHILDHOOD*

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In collaboration with Monti,¹ I found that 95 per cent. of the children of the poor in Vienna showed evidence of a tuberculous infection at the time of puberty. Since then a number of papers on this subject have appeared from various cities and countries. The results were very different. The cause of this variation lies partly in the actual differences in the various cities, but to a certain extent the difference in the method used for the examination and the difference in the selection of the material share the responsibility.

I regard it necessary that the important question of the spread of tuberculosis in definite cities, countries and strata of society should be answered definitely. To this end it is absolutely necessary to use the best methods of examination and to select the material properly.

SELECTION OF MATERIAL

A true picture of the actual conditions can only be obtained by examining either all children of a certain age, or all children, which is hardly possible. The examination of school children means a selection which can be regarded as free from objection and so does the examination of children attending public kindergartens. The examination of children in infectious disease hospitals can also be used because it is permissible to assume that children with or without tuberculosis acquire diphtheria or scarlet fever with equal readiness. Figures obtained in a scarlet fever or diphtheria ward surely may be regarded as representative of the actual conditions, but it is not permissible to use results obtained in a dispensary for the preparation of statistics. This material includes many more tuberculous children than the average. Tuberculous children tend to concentrate there and the figures become too high. For this reason the figures which Von Pirquet gave in his first statistic based as they were on the material of the dispensary of the Vienna Kinder Klinik cannot be accepted; and many contributions of other investigators share this fate.

TUBERCULIN METHOD

It is not sufficient to exercise proper care in the selection of the material but the tests have to be made with a reliable method. Only

* Received for publication, March 18, 1922.

1. Hamburger and Monti: München. med. Wchnschr. **56**:450, 1909. Monti: Wien. med. Wchnschr. **62**:447, 1912; Wien. klin. Wchnschr. **21**:1407, 1908.

then can the frequency of tuberculosis be established. The justification of such a demand is self-evident. Nobody will doubt its principle in the least. In spite of this many papers dealing with the frequency of tuberculosis in different cities and countries reveal the fact that, quite generally, a tuberculin method has been used which is entirely unreliable, having an error as high as 40 per cent. This method is the cutaneous tuberculin test of Pirquet. The main purpose of this paper is to call attention to the fact that this method is inexact and therefore misleading. It gives figures which are far too low.

The method of Pirquet is very simple. It rapidly gained great favor and was used widely. Many papers are published which are based entirely on the Pirquet method, but the results are wrong because the method is inexact. Twelve years ago, Reuschel,² and shortly afterward I, called attention³ to this fact. It was shown that the local subcutaneous reaction (so-called Stichreaction) gives much more reliable results. I have called attention again and again to this unreliability of the Pirquet reaction and particularly in my monograph on tuberculosis in childhood, but, I regret to say, without much success.

A comparison of the figures obtained by Pirquet with his cutaneous method with those obtained by Monti and myself with the local subcutaneous method demonstrates the degree of error of the cutaneous reaction. Vienna furnished the material for both statistics. Pirquet found in children from 11 to 14 years of age an incidence of tuberculosis of only 56 per cent.; we found 95 per cent., i. e., 40 per cent. more. At that our figures were obtained from a material (hospital for infectious diseases) in which rather less tuberculous infection was to be expected than in the material of Pirquet (dispensary). Only very few authors confirmed the statements of Reuschel and myself (Nothmann,⁴ Pirquet,⁵ Rominger⁶). Occasionally the intracutaneous method of Mantoux has been employed, but not frequently. This method has no advantages over the subcutaneous method and at times the dosage remained insufficient. In order to exclude tuberculosis, the reaction must remain negative with from 1 to 10 mg.

The method I worked out in detail is this: All children to be examined are first subjected to a cutaneous or percutaneous test with concentrated tuberculin.⁷ Those who do not react, from twenty-four to forty-eight hours later, receive a subcutaneous injection of 0.01 mg.

2. Reuschel: München. med. Wchnschr. **55**:330, 377, 1908.

3. Hamburger: Wien. klin. Wchnschr. **21**:381, 1908.

4. Nothmann: Berl. klin. Wchnschr., 1910, No. 9.

5. Pirquet: Ergebn. d. inn. Med. u. Kinderh. **5**:

6. Rominger: Monatschr. f. Kinderh. **18**:424, 1920.

7. With the percutaneous inunction method of Moro more positive results are obtained if the original tuberculin is evaporated on the waterbath ad maximum (F. Hamburger and F. Stradner: München. med. Wchnschr. **45**:243 [Feb. 27] 1919).

tuberculin. Those who do not react after the second injection are given a third injection after a further twenty-four hours. If the test is negative, another injection is given after the lapse of another twenty-four hours, or at most forty-eight hours, the dosage being raised to 1 mg. If the place of injection does not show any reaction, such as definite redness and infiltration, the child may be regarded as free from tuberculosis with nearly absolute certainty. In doubtful cases, an injection of 10 mg. is given.

It is evident that this method is time consuming and bothersome. In schools and similar public institutions it meets with opposition. The cutaneous or percutaneous method, on the other hand, is very simple in its execution and does not meet with opposition. A cumbersome method of examination competes with a simple one, but the cutaneous method is absolutely unreliable and the subcutaneous method is reliable. It cannot be the object of scientific investigation to find out how many individuals of a given age give a positive cutaneous reaction, but solely how many children of a given age are infected with tuberculosis. The cutaneous method cannot be used comparatively on the assumption that the percentage of its error remains constant. The results of this method are too dependent on a variety of circumstances: (1) The kind of instruments used (Pirquet's "Bohrer," scalpel, vaccination lancet, needle) and the depth of the wound. (2) The length of time the tuberculin acts. (3) The activity of the tuberculin. The different series of the same firm have by no means a constant activity. (4) Whether the cutaneous test has been made once or repeatedly. In the latter case more positive results are obtained. (5) The time of the year seems to exercise some influence on the reaction.⁸

Sufficient data, I believe, have been given to show that the cutaneous reaction cannot alone be used to determine the frequency of tuberculosis. The cutaneous or percutaneous method should be employed first and only when these reactions are negative the subcutaneous method just described should be used.

SUMMARY

To determine the frequency with which tuberculous infection has occurred in various periods of childhood, it is necessary (1) to select properly the material to be examined. The test can be done in children from schools or kindergartens or from infectious disease hospitals, but not in children from dispensaries. (2) To choose the proper method of applying the tuberculin test. The only suitable method is the subcutaneous injection (from 1 to 10 mg.) after a preceding cutaneous or percutaneous application. The cutaneous or percutaneous method alone cannot be used.

8. Hamburger: München. med. Wchnschr. 67:398, 1920.

Ar. or 2-125. Child.
20484, 1922

IDIOPATHIC APLASTIC ANEMIA *

REPORT OF CASE IN A CHILD FOUR YEARS OLD; MARKED
IMPROVEMENT FROM TRANSFUSION

CHARLES HERRMAN, M.D.

NEW YORK

REPORT OF CASE

M. L., female, aged 4, was admitted to Lebanon Hospital Nov. 4, 1921.

Family History.—Parents apparently healthy; no history of tuberculosis or syphilis; no members of the family have had any diseases of the blood or the blood forming organs. Patient has one sister who is healthy.

Personal History.—Full term, normal delivery; breast fed; normal physical and mental development during infancy. Measles at 2 years of age, no complications.

Present Illness.—During the past two weeks she has had fever, has become more and more pale and weak; complained of pain in the abdomen.

Physical Examination.—Child apathetic; marked grayish white pallor; puffiness of the face, especially the eyelids; all the mucous membranes are very pale. Sclera bluish, not yellowish. No distinct enlargement of the lymph nodes.

Heart: No murmur, no marked enlargement; regular but rapid (130).

Lungs: Negative.

Abdomen: Negative; liver and spleen not enlarged.

Extremities: On the back of the left calf is an ecchymotic spot 2 cm. in diameter.

Examination of the Blood.—November 4: hemoglobin (Dare) 25 per cent.; red blood cells, 750,000; white blood cells, 2,500; polymorphonuclears, 25 per cent.; lymphocytes, 72 per cent.; no myelocytes. The red cells show slight changes in form, size and color. No nucleated red cells. The results of the examination of the blood at various times are given in Table 1.

Clinical Course.—As the child appeared to be moribund, she received a transfusion of 380 c.c. blood (father). To our great surprise she rallied, and made a gradual but progressive improvement.

November 7: Distinct improvement, less pallor, apathy and irritability; improvement in appetite. Pirquet and Wassermann tests negative. Examination of fundus (Dr. Barnert): no hemorrhages. Urine: acid; specific gravity, 1.014; trace of albumin; occasional hyaline cast and a few white blood cells; no urobilin. Feces: no blood, parasites, or ova.

ROENTGENOLOGIC EXAMINATION (Dr. Scholz)—Chest: moderate swelling of the root glands; slight increase in upper mediastinal shadow; moderate enlargement of the heart to the left. Arm: increased porosity of the bones, moderate diffuse atrophy.

November 11: Rise in temperature to 106 F., no apparent cause.

November 12: Spleen just palpable.

November 16: Spleen distinctly palpable.

November 14: Rise in temperature to 105.5 F.; no visible cause.

November 16: A large ecchymotic spot appeared on the left side of the neck 3 cm. in diameter.

November 18: Tonsils red and slightly enlarged.

* Received for publication March 20, 1922.

* Read at the Annual Meeting of the American Pediatric Society, held at Washington, D. C., May 1-3, 1922.

The patient was discharged Dec. 3, 1921, very much improved. In the latter part of December she had a mild attack of tonsillitis from which she recovered without any apparent injurious effect on her general condition or blood.

Name.—In addition to aplastic anemia, a number of different names have been given to this condition by different authors: aregeneratory anemia (Pappenheim); hemolytic aplastic anemia (Turk); aleukie

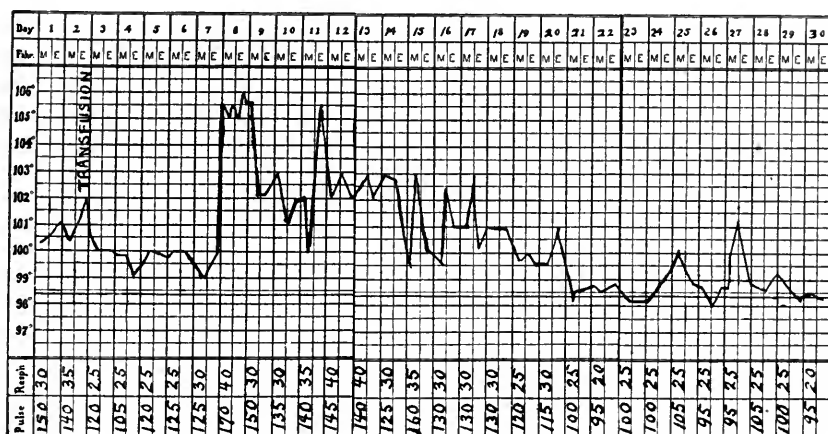


TABLE 1.—RESULT OF BLOOD EXAMINATIONS

Date	Hb. per Cent.	R. B. C.	W. B. C.	Poly- morpho- nuclears, per Cent.	Lym- pho- cytes, per Cent.	
Nov. 4, 1921	25	750,000	2,500	25	72	Slight poikilocytosis and polychromatophilia; few macrocytes; no nucleated red cells or myelocytes
Nov. 5, 1921	20	800,000	2,500	Slight poikilocytosis and anisocytosis; no nucleated red cells or myelocytes
Transfusion Nov. 7, 1921	45	2,330,000	2,400	22	65	Platelets. 170,000; coagulation time, 8 min. (Lee-White)
Nov. 13, 1921	43	2,700,000	2,300	40	55	Bleeding time, 10 min. (Duke); fragility normal; complete, 0.36
Nov. 24, 1921	47	2,500,000	3,500	36	60	Slight poikilocytosis and anisocytosis; no nucleated red cells or myelocytes
Dec. 3, 1921	65	3,800,000	6,000	47	50	

hemorrhagica (Frank). Schneider proposes the terms toxic paralytic anemia and toxic anhemopoietic anemia, because aplastic implies a congenital deficiency, and aregeneratory implies a poorly developed marrow readily failing on demand. However, the term aplastic anemia has been so generally used that it seems best to retain it.

TABLE 2.—ANALYSIS OF CASES OF APLASTIC ANEMIA IN CHILDREN

Author	Sex	Age	Duration	Hb., %	R. B. C.	W. B. C.	Polymorpho-nuclears		Mar-row
Acona.....	♀	9	1 mo.	..	1,500,000	4,200			
Babonneix and Paiseau	♂	11	6 wk.	25	510,000	4,800	24	Slight anisocytosis and poikilocytosis; no nucleated red cells or myelocytes; few macrocytes	Fatty
Babonneix and Tixier ¹	♀	5	3 mo.	15	380,000	2,000	24	No anisocytosis, poikilocytosis, polychromatophilia, nucleated red cells or myelocytes	
Babonneix and Tixier ¹	♂	11	1 yr.	15	550,000	1,200	34	Slight anisocytosis; no poikilocytosis, polychromatophilia or nucleated red cells	Fatty
Benecke ²	♂	6	Recovery	12	440,000	1,600	42	Slight anisocytosis; no poikilocytosis or nucleated red cells	
Gorter.....	♂	6	3 wk.	17	700,000	1,600	12	Anisocytosis; no polychromatophilia, nucleated red cells or myelocytes	Fatty
Herrman.....	♀	4	Recovery	25	750,000	2,500	25	No anisocytosis, poikilocytosis, polychromatophilia, nucleated red cells or myelocytes	
Heubner.....	♂	2	6 mo.	10	980,000	7,800	..	Anisocytosis; no poikilocytosis, polychromatophilia or nucleated red cells	Fatty
Kharina ³	♀	2½	12	630,000	7,800	43	Slight anisocytosis and poikilocytosis	
Kleinschmidt ⁴ ..	♀	8	6 mo.	10	1,000,000	3,000	13	No anisocytosis, poikilocytosis or polychromatophilia; few nucleated red cells	Hypo-plastic
	♂	10	6 mo.	23	1,200,000	1,800	28		
	♂	12	4 mo.	35	2,000,000	2,800	11	Poikilocytosis; no nucleated red cells	
Larrabee.....	♀	4½	21 mo.	22	820,000	5,800	36		Fatty
	♂	5	1 yr.	25	1,500,000	5,000	3.2	No anisocytosis, poikilocytosis or nucleated red cells	
Muir.....	♂	14	3 mo.	12	640,000	7,000	25	Slight poikilocytosis; no nucleated red cells or myelocytes	
Parkinson ⁵	♂	9	Recovery	20	580,000	2,600			
Rennie ⁶	♀	13	3 mo.	20	720,000	3,800	5	No anisocytosis, poikilocytosis, nucleated red cells or myelocytes	
Silva.....	♂	12	3½ mo.						
Smith ⁷	♂	6	8 mo.	10	400,000	4,000	25	Poikilocytosis; anisocytosis; achromatocyte	Fatty
Spak ⁸	♂	4							
Türk.....	♂	12	4 mo.	11	500,000	4,280	32	Slight anisocytosis, poikilocytosis and polychromatophilia; no nucleated red cells or myelocytes	
Thursfield ⁹	♀	11	7 mo.	30	1,140,000	5,200	35		Fatty

1. Babonneix and Tixier: Bull. et mém. Soc. méd. d. hôp. de Paris, **35**:227, 1913.

2. Benecke: Therap. d. Gegenw. **19**:14, 1917.

3. Kharina-Marinucci: La Pediatria **23**:101, 1915.

4. Kleinschmidt: Jahrb. f. Kinderh. **81**:1, 1915.

5. Parkinson: Proc. Roy. Soc. Med. Lon. **11**:55, 1917 (Sect. Dis. Child.); **12**:72, 1918 (Sect. Dis. Child.).

6. Rennie: Med. J. Australia **1**:485, 1919.

7. Smith: Am. J. Dis. Child. **17**:174 (March) 1919.

8. Spak: Acta Paediatrica **3**:310 (Dec. 15) 1921.

9. Thursfield: Brit. M. J. **2**:873, 1921.

Frequency.—About eighty cases of this condition have been reported. Of these twenty-one occurred in children. However, I have no doubt that with more careful observation and hematologic study the disease will be found to be less rare than the number of reported cases would seem to indicate.

Sex.—About an equal number of cases have occurred in each sex in adults; in children, however, twice as many occurred in males as in females: fourteen males, seven females. Only one case has been reported in an infant, that of Heubner.

Etiology and Pathogenesis.—Although many hypotheses have been advanced, very little is known at present as to the causation of this condition. The most generally accepted explanation is that it is a primary lesion of the bone marrow due to the action on it of some unknown toxic material. This results in a deficient production of blood cells, red cells, polymorphonuclear leukocytes, platelets and myelocytes. There is no definite evidence that the reduction in the red cells is due to increased destruction. The urine is free from urobilin; the skin is not icteric; the serum is not darker than normal in color; in the blood there is usually an absence of poikilocytosis; the color index is rarely above 1. In the liver there is usually no marked deposit of hemosiderin. The family history is usually negative as far as disease of the hemopoietic system is concerned. In only a very few cases is there a history of tuberculosis or syphilis.

In a few the disease has followed an acute infection. Smith considers the possibility in his case that "the prolonged toxic action of the toxin of measles, acting in a cumulative sort of fashion, until the marrow became exhausted" might have caused the condition, but when it is considered that practically all children have measles, that, therefore, even the rarer complications are not uncommon, it seems strange that if aplastic anemia bears some relation to the disease it should be so rare. It would have to be assumed that the particular patient had a congenital or acquired inferiority of the bone marrow. Of course, such an inferiority might be latent, and only brought to light by an attack of some acute infectious disease, such as measles. As a matter of fact, several authors have suggested the possible presence of such an inferiority in these cases, and a few patients were anemic from birth or at a very early age. In two of Schneider's three cases a "status lymphaticus" was found at necropsy.¹⁰ Türk has suggested a possible relation to hypoplasia of the blood vessels and genitals. However, the majority of the patients reported were apparently well until the onset

10. Moore and Keidel noted that secondary apastic anemia following the injection of arsphenamin, was more common in patients with the lymphatic diathesis.

of the disease. Kleinschmidt⁴ considered carefully the possible presence of a constitutional peculiarity or inferiority in his patients, but could find no definite evidence.

Pathology.—Characteristic changes are found in the skin, mucous membranes, liver and spleen; and pathognomonic changes in the bone marrow. In the skin petechial hemorrhages or ecchymotic spots of greater or less extent. Hemorrhage from any or all the mucous membranes, and the serous coverings of the viscera. Various organs, principally the heart muscle, liver, kidneys show fatty degeneration. A marked deposit of hemosiderin is rarely found in the liver. The bone marrow is largely replaced by fat and connective tissue, which gives it a yellow color and a peculiar consistency. A small remnant of normal or even compensatory hyperplastic marrow may occasionally be found, but the red color may be due to small hemorrhages. On examination the marrow shows an absence of normoblasts, megaloblasts, and myelocytes, the predominating cells being lymphoid.

Symptomatology.—The disease manifests itself by anemia, shortness of breath and general weakness. The skin and conjunctiva are not yellow; the former is grayish white, the conjunctiva has a bluish tinge. A puffiness of the face, more especially the eyelids is frequently noted. There may be pain in different parts of the body, but there is no definite pain on pressure over the bones. Fever may be present, sometimes marked without discoverable cause.

There is usually a distinct hemorrhagic tendency as shown by the appearance of petechial spots on the skin, and in many cases hemorrhages from various mucous membrane surfaces. Retinal hemorrhages are not uncommon. In many cases a systolic murmur is heard at the base of the heart; no characteristic changes are found in the lungs. The liver, spleen and lymph nodes are not usually enlarged. As a rule, there are no marked nervous symptoms, unless the disease is associated with complications.

The urine does not contain urobilin. Occasionally a trace of albumin, and a few hyaline casts may be present.* When there is hemorrhage in any part of the digestive tract the stools will contain blood. Roentgenologic examination of the bones may reveal changes in texture; and with improved technic it is not unlikely that much valuable information will be obtained in this way. In Muir's case there was found at necropsy a thickening of the cortex of the bone, and a diminution in the size of the medullary canal. In my own case there was an increased porosity, as shown by the less dense shadow.

The changes in the blood are characteristic. There is a marked diminution in the percentage of hemoglobin, the number of red and white blood cells. The reduction in the leukocytes is chiefly at the expense of the polymorphonuclears. As a rule, there are no normo-

blasts or megaloblasts and no myelocytes. The form, size and color of the red cells is not usually changed. The number of platelets is diminished, sometimes very markedly. The bleeding time is increased. The coagulation time is normal, but there is an imperfect retraction of the clot. The fragility of the red cells is normal as tested with hypotonic saline solutions. Blood cultures are negative.

The anemia and general weakness, together with the hemorrhagic tendency, usually become progressively worse, and the patients die from asthenia or some intercurrent complication.

Diagnosis.—In a fairly typical case it should be possible to make a tentative diagnosis during life, from the anemia with its characteristic blood changes; but an absolutely certain diagnosis must, of course, rest on the finding of the pathognomonic changes in the bone marrow as revealed by necropsy. Minot believes that the disease may bear some relation to purpura hemorrhagica. In both conditions there is a diminution in the number of platelets with the accompanying hemorrhagic tendency, but in many cases of aplastic anemia the anemia is marked before any severe hemorrhages have occurred, as in my own case; and in purpura hemorrhagica, the polymorphonuclear leukopenia is absent (Table 3). If the patient is under observation for any length of time it will usually not be difficult to differentiate the condition from an aleukemic phase of a lymphatic leukemia. The severe secondary anemias of the Von Jaksch type occur almost always in infants. They are associated with an enlarged spleen and an entirely different blood picture. The latter shows evidence of increased bone marrow activity.

The disease from which it is most important and difficult to differentiate aplastic anemia is pernicious anemia (Table 3). In fact, some authors still describe aplastic anemia as a form of pernicious anemia. However, the majority now recognize it as a distinct condition. Pernicious anemia is exceedingly rare in young children. In many of the reported cases the diagnosis is doubtful. Some years ago, Monti and Berggrün collected sixteen cases including one of their own. Of these only a few cases were verified by postmortem examination, including an examination of the marrow. In many of the remaining cases the clinical, including the blood, findings are very incomplete. Even in some of those cases in which the data are complete the diagnosis may be considered doubtful. For example, a case is reported by Escherich in which the symptoms were: anemia, general weakness, blood in the stools. Blood: hemoglobin, 10 per cent.; red blood cells, 575,000; white blood cells, 7,000 (on one examination, 3,500); marked reduction in polymorphonuclears. Slight changes in the form, size and color of the red blood cells, but no nucleated cells. A reduction in the platelets. A necropsy was not held.

The differential diagnostic points in these two diseases are given in Table 3, the chief being the difference in the color of the skin, the absence of urobilin in the urine, the blood picture with its absence of evidence of bone marrow activity, the absence of increase in the number of platelets following the injection of epinephrin, the positive constriction test, the increased bleeding time, the usually lower color index, and the diminished bilirubin content.

TABLE 3.—DIFFERENTIAL DIAGNOSIS BETWEEN PERNICIOUS ANEMIA, APLASTIC ANEMIA AND PURPURA HEMORRHAGICA (ESSENTIAL THROMBOPENIA—GORKE¹¹)

	Pernicious Anemia	Aplastic Anemia	Purpura Hemorrhagica
I. General Symptoms:			
Color of skin.....	Straw yellow.....	Alabaster white, cadaveric	Good, to extreme pallor
Hemorrhage of skin and mucous membrane	Unusual.....	Usually marked.....	In crops with free intervals
Mouth.....	Tongue smooth, edges atrophic; vesicles	Unchanged tongue; gingivitis; stomatitis; necrotic angina	Petechial hemorrhages; usually gingivitis
Spleen.....	Usually moderate enlargement	Not enlarged.....	May be enlarged
Urine.....	Urobilin present.....	Urobilin absent.....	Urobilin occasionally present
Secretion of gastric juice	Diminished.....	Occasionally diminished	Normal
Stools.....	Urobilin present.....	Very little urobilin.....	Normal
II. Blood:			
1. Morphology:			
(a) R. B. C.	Diminished number; anisocytosis; polychromatophilia; normoblasts; megaloblasts	Markedly diminished; no change in form; no nucleated red cells; no erythroblastic reaction	Variable; sometimes polycythemia; few young forms
(b) W. B. C.	Leukopenia; often relative lymphocytosis	Leukopenia; marked reduction of polymorphonuclears	Often leukocytosis; no change in differential count
(c) Platelets*.....	Diminished; epinephrin causes increase; splenectomy causes increase	Diminished; epinephrin and splenectomy cause no increase	In attacks marked thrombopenia; epinephrin and splenectomy increase
2. Constriction test†	No petechia.....	Hemorrhage, skin.....	Hemorrhage, skin
3. Bleeding time.....	Normal.....	Increased.....	Increased in attack
4. Retraction clot.....	Normal.....	Imperfect.....	Imperfect
5. Katalase index.....	Increased.....	Normal.....	Normal
6. Color index.....	Over 1.....	Usually 1.....	Under 1
7. Fragility, coagulation time	Normal.....	Normal.....	Normal
8. Bilirubin content...	Increased.....	Diminished.....	Normal

* The epinephrin test is made by injecting 1 mg. epinephrin, comparing the platelet count before and after the injection.

† The constriction test is made in the usual way by constricting the arm with a band and noting if hemorrhage results.

‡ The katalase index is normally between 6.1 and 6.8. It depends on the presence of a ferment which splits up hydrogen peroxid into water and oxygen.

The postmortem findings in these two diseases are distinct. In pernicious anemia there is a hyperplasia of the bone marrow; the production of new cells fails to keep up with destruction. In aplastic anemia there is an aplasia, or at least a hypoplasia, of the marrow. There is deficient production of new cells, but no evidence of increased destruction. In pernicious anemia there is a marked deposit of hemosiderin in the liver and the body fat is canary yellow; in aplastic anemia there is rarely a hemosiderin deposit, and the body fat is not canary yellow.

Prognosis.—In those severe cases in which the disease has come on suddenly, so that the time of onset is definitely known, the duration has been from one to three months. Mostly all authors consider the disease as being invariably fatal. This may be true for adults, but in children there appears to be a less acute form from which recovery is possible. Such a case is reported by Parkinson⁵ and another by Benecke.² In my own case, the time elapsed is still too short to speak of a cure.¹⁰ In Larrabee's case¹¹ there was a remission of several months. In the child we are dealing with a growing organism; the hemopoietic system is particularly active, so that if there is a marked hypoplasia rather than an aplasia, the possibility of regeneration is conceivable. In Parkinson's and Benecke's cases, and in my own case, the gradual but progressive improvement in the blood picture, together with the improvement in the appearance, temper and appetite would tend to show that regeneration is possible in the less acute, malignant form of the disease. The permanency of the improvement in the blood picture following transfusion is a good indicator of prognosis. It is interesting to note that in the secondary aplastic anemia following roentgen-ray exposure, and the injection of arsphenamin, although the characteristic changes are present in the blood, if roentgen-ray treatment or arsphenamin injections are discontinued, regeneration is possible and the patient may recover.

Treatment.—Preparations of iron, so valuable in other forms of anemia, are of little or no value in this form. A few patients have been somewhat benefited by injections of arsenic. Benecke's patient received "solarson," an arsenic preparation used at Klemperer's clinic, and recovered. Preparations of bone marrow have been given without any favorable effect. Radiation of the bone with the roentgen ray may be injurious rather than beneficial. The best method at our command at present is transfusion of whole blood. The investigations of Unger and others would seem to make it advisable to use the blood without the addition of sodium citrate. From 300 to 500 c.c. are usually given and repeated if necessary. In this way the platelets are at least temporarily increased and the hemorrhagic tendency is diminished. Fresh blood is supplied to the organism, and in some cases at least this seems to have also a stimulating effort on the bone marrow. If after a temporary improvement, the blood rapidly tends to return to its previous condition, the outlook is unfavorable; however, if a slight but progressive increase in the percentage of hemoglobin, in the number of red blood cells, in the polymorphonuclear leukocytes and in the platelets takes place, the prognosis is not unfavorable. In such cases there are probably still some small areas of normal marrow which may be reac-

10. The patient died at home April 25, 1922; no necropsy was obtained.

11. Larrabee: J. A. M. A. **75**:1632 (Dec. 11) 1920.

tivated so that the patient is tided over the danger period. Splenectomy has been performed in one or two cases with unfavorable result. It appears to be contraindicated.¹²

12. Smith⁷ gives a fairly complete bibliography up to 1918. The following may be added: Benjamin: *Verhandl. d. Gesellsch. f. Kinderh., Karlsruhe*, 1911. Frank: *Berl. klin. Wchnschr.* **37**:961, 1915. Helly: *Prag. med. Wchnschr.* No. 52, 1908. Irisawa and Koga: *Mitt. a. d. med. Fakult. d. k. Univ. z. Tokyo* **18**: 179, 1918. Symmers: *Interstate M. J.* **24**:1103, 1917. Westenrigk: *Russk. Vrach.* No. 36, 1912. Glenn and McVey: *Northwest Med.* **18**:65, 1919. Gorke: *Deutsch. Arch. f. klin. Med.* **136**:143, 1921. Jerosch: *Med. Klin.* **16**:1058, 1920. Musser: *M. Clin. N. America* **3**:1416, 1919. O'Malley and Conrad: *J. A. M. A.* **73**:1761 (Dec. 6) 1919. Von Willebrand: *Finska läk.-sällsk. handl.* **60**:859, 1918.

SPASMOPHILIA AND THE ALKALI RESERVE OF THE BLOOD *

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AND

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Wilson and his co-workers¹ pointed out that in parathyroidectomized dogs, just previous to the attacks of tetany, an increased alkalinity of the blood develops, a condition termed by them "alkalosis," which is neutralized by the acid products generated by the tetanic contractions of the musculature. Recently Grant and Goldman² have shown that forced respiration may cause symptoms of tetany to appear in the human. In these cases the underlying factor appears to be an "alkalosis." The forced breathing causes an excess of carbon dioxide to be exhaled from the lungs, thereby reducing the amount in the blood. This results in an increased alkalinity of the blood. However, they observed that the tetanic movements apparently produce acid products which tend to compensate for the increased alkalinity until a readjustment takes place.

Clinically it has at times been noted³ that after the therapeutic administration of sodium bicarbonate for acidosis, characteristic symptoms of tetany may develop. These symptoms cease promptly when the sodium bicarbonate is stopped.

Howland and Marriott³ have made determinations of the hydrogen ion concentration of the serum of infants with tetany by the dialysis indicator method, but have not found an "alkalosis."

Acute infections frequently precipitate active manifestations of spasmophilia in those having the latent form previous to the infections. As acute infections are usually accompanied by a tendency to acidosis, alkalosis could scarcely be a factor in producing tetany in this type of case.

Jones and Nye⁴ found no relation between the alkali reserve and the concentration of calcium and phosphoric acid in the blood. Other investigators believe that the hydrogen ion concentration of

* Received for publication, Feb. 25, 1922.

* From the Department of Pediatrics, University of Illinois, and Children's Department, Cook County Hospital.

1. Wilson, Stearns and Thurlow: *J. Biol. Chem.* **23**:89, 1915. Wilson, Stearns and Janney: *ibid.* **23**:123, 1915.

2. Grant, S. B., and Goldman, A.: *Am. J. Physiol.* **52**:209, 1920.

3. Howland, J., and Marriott, W. McK.: *Quart. J. Med.* **11**:289, 1917.

4. Jones, M. R., and Nye, L. I.: *J. Biol. Chem.* **47**:331, 1921.

the serum (and the factors regulating this as the carbon dioxid tension and the alkali reserve) influence the type of calcium and phosphate salts formed, and consequently the relative amounts of calcium and phosphate ions available and the solubility of their salts.⁵

We determined the carbon dioxid combining power of the blood plasma by the Van Slyke method⁶ in several cases of active spasmophilia in infants and again after their recovery.

REPORT OF CASES

The following are the histories, in abstract, of the patients we have studied:

CASE 1.—G. D., aged 15 months, colored, weight 14 pounds, was admitted to Cook County Children's Hospital, April 3 with evidence of an early bronchopneumonia and signs of active tetany consisting of marked laryngospasm, Chvostek, Trousseau and an Erb's electrical reaction of C.O.C.=3.5 ma. There were also signs of marked rickets. The tetany cleared up on treatment with calcium bromid, and cod liver oil with phosphorus, and was reprecipitated by a course of sodium chlorid, 15 grains, and potassium citrate, 10 grains, given once daily. Six days after starting the sodium and potassium salts there was a definite Chvostek, a moderate Trousseau and a C.O.C. of 2.5 ma. Blood was drawn at this time from the longitudinal sinus to be examined by the Van Slyke method for a determination of the carbon dioxid combining power, and it was found that there were 40 c.c. of carbon dioxid bound as bicarbonate by 100 c.c. of plasma. The patient was again placed on calcium lactate, 3 grains, twice daily, and cod liver oil with phosphorus, 1 dram, three times daily, after stopping the sodium and potassium salts. At the end of six days of this treatment, the C.O.C. was 15 ma., there was no carpopedal spasm and only a very faint Chvostek. The blood reading showed 53.3 c.c. of carbon dioxid bound as bicarbonate by 100 c.c. of plasma. Eighteen days later there were still no clinical manifestations of spasmophilia and the blood reading was 46.2 c.c. of carbon dioxid.

CASE 2.—E. M., aged 3 years, colored, weight 17 pounds, was admitted May 23, 1921, suffering from pertussis, very marked rickets and active tetany consisting of marked laryngospasm, Chvostek and C.O.C. of 4 ma. with generalized convulsions. The next day the child was placed on 1 dram of phosphorized cod liver oil and calcium lactate, 5 grains, three times daily, and antispasmodics for the pertussis. The day that this treatment was instituted the blood reading was 42.4 c.c. of carbon dioxid, the spasmophilic signs were the same, although no convulsion had occurred during the previous eighteen hours. The C.O.C. was 3.5 ma. On examination twenty-two days later there were no signs of spasmophilia; C.O.C. 12 ma., and the blood⁷ reading was 59 c.c. of carbon dioxid. Nine days later there were still no clinical manifestations of tetany, and the blood reading showed 55.3 c.c. of carbon dioxid combined as bicarbonate to 100 c.c. of plasma.

CASE 3.—M. M., twin of E. M., was admitted the same day and with the same clinical findings but no generalized convulsions. C.O.C.=4 ma. The blood reading on admission was 47 c.c. of carbon dioxid. After having been on cod liver oil and calcium lactate for eleven days with no signs of tetany, the blood⁷ reading was 50 c.c. of carbon dioxid.

5. Howland, J., and Kramer, B.: *Am. J. Dis. Child.* **22**:105 (July) 1921.

6. Van Slyke, D. D., and Cullen, G. E.: *J. Biol. Chem.* **30**:317, 1917.

7. The blood was obtained from the external jugular vein.

CONCLUSIONS

In the cases of spasmophilia in the infants studied, no evidence of "alkalosis" was found. In fact, there was a tendency for the alkali reserve to be lowered during the spasmophilic stage and gradually to be increased as the cases recovered.

It appears that the symptoms of tetany may be produced in a variety of ways, but the evidence is not forthcoming that "alkalosis" plays a part in the genesis of infantile spasmophilia.

We wish to thank Dr. Welker and the Department of Physiological Chemistry of the University of Illinois for the privilege of using their laboratories for the blood chemistry work.

ACTIVE IMMUNIZATION OF NURSES AGAINST DIPHThERIA IN A CHILDREN'S HOSPITAL *

J. V. COOKE, M.D.

ST. LOUIS

The immunization of children against diphtheria by toxin-antitoxin mixtures has been carried out on a considerable scale with excellent results. Two of the more recent series in which the immunity was confirmed by later Schick tests are those reported by Zingher¹ and by Blum.² Such immunization has been advised for susceptible physicians and nurses, especially those caring for children, since they are more intimately exposed to diphtheritic infection. No studies on groups of adults, however, have been reported. Herewith are presented the results of a systematic immunization of all the susceptible individuals in a nurses' training school over a period of years. All the individuals were on duty in the Contagious Pavilion of the St. Louis Children's Hospital during a part of their training, usually from one to two months, and the incidence of diphtheria in the group before and after the immunization was instituted has been noted.

METHODS

The toxin for Schick tests and the toxin-antitoxin mixture used were obtained through the New York City Board of Health. Beginning in 1918, Schick tests were performed on all pupil nurses of the Washington University Training School, except those who had completed their service on the contagious wards. Subsequent entrants were tested when admitted. The nurses reported in groups of from six to fifteen so that any given group furnished both positive and negative reactions. In every case a control of the same amount of toxin heated to 75 C. for five minutes was also done. Readings were made at the end of two and four days and a final observation was made on the sixth or seventh day. Any definite reaction at that time was considered positive. A strongly positive reaction was designated ++, one of moderate intensity + and a faint positive reaction ±. All nurses who gave positive reactions were immunized by three subcutaneous injections of toxin-antitoxin mixture (3 L. + doses + 3½ units), given at intervals of one week, and the Schick test was repeated four months later.

* Received for publication, March 9, 1922.

* From the Department of Pediatrics, Washington University School of Medicine, and the St. Louis Children's Hospital.

1. Zingher, A.: Active Immunization of Infants Against Diphtheria, *Am. J. Dis. Child.* **16**:83 (Aug.) 1918.

2. Blum, J.: Active Immunization Against Diphtheria in a Large Child-Caring Institution, *Am. J. Dis. Child.* **20**:22 (July) 1920.

Before giving the results of the study, brief mention may be made of certain general observations concerning the tests. Pseudoreactions were noted in 38 per cent. of sixty-one negative Schick tests, but in these are not included some slight reactions of about 1×1 cm. consisting of a faint erythematous blush which persisted for two or three days. The largest pseudoreaction measured 8×13 cm. with the central deeper red area 2×2 cm. in size. Some of the more intense pseudoreactions did not fade completely even at the end of a week and a faint brownish pigmentation remained. Combined reactions were shown in about 20 per cent. of the positive tests. Since readings were made at intervals on all the tests, there was opportunity to observe whether the reading on the second day differed from that on the later examinations. In nineteen instances out of 222 there were well marked changes in the test, some fading while others became more intense. Ten tests which were $+$ or \pm on the second day became more marked at the end of four days, while three cases which were $-$ became $+$; in four instances a $+$ reaction became \pm , and two \pm reactions had faded completely in four days and were read $-$. These changes were quite independent of any pseudoreactions in the controls.

The reactions following the injections of toxin-antitoxin, as a rule, were somewhat similar to those following prophylactic typhoid vaccination. Usually there was a well marked local redness, swelling and tenderness of an area several cubic centimeters in diameter persisting for from twenty-four to forty-eight hours. Many remembered some listlessness and headache when questioned a week later. In only two individuals was the effect at all severe. A marked general reaction with a chill and temperature of 103 F. followed the injection, with general malaise and headache continuing from three to four days. The arm was greatly swollen from elbow to shoulder with a large area of red and purplish discoloration at the site of injection, accompanied by marked tenderness and disability. A similar reaction followed each injection.

In all, Schick tests were performed on 147 nurses of whom sixty-one, or 41.5 per cent., gave negative reactions and eighty-six, or 58.5 per cent., gave positive reactions. Of the latter, thirty-nine were $++$, thirty-seven were $+$ and ten were \pm . This high percentage of positive reactions was unexpected and differs considerably from the figures usually given for adults (about 30 per cent.). The relative proportion of positive and negative reactions was remarkably constant, however, in the separate groups tested and did not vary in the different years.

One possible explanation for the high incidence of susceptible individuals in this group of nurses is that the majority of them were reared in small communities where diphtheria is far less prevalent than in cities. There is considerable evidence that contact with diphtheria

cases plays an important part in the development of an antitoxic immunity. The morbidity statistics in Pennsylvania,³ for example, during the years 1916-1918 show that diphtheria was much more prevalent in urban than in rural communities, the relative proportion being 530 in the urban to 370 in the rural. The figures quoted by Zingher,⁴ from the examination of school children show conclusively that children from congested districts in cities show a much higher percentage of immunes than those from more sparsely settled sections and rural communities. The percentage of positive Schick tests usually given for adults is considerably lower than that found in children, and it seems quite probable that this increased immunity in later life depends, at least in part, on contact with diphtheria organisms since the antitoxin is a specific antibody. In the larger cities diphtheria is endemic, and each year there is a large morbidity. In St. Louis, for example, the morbidity is about 0.5 per cent. of the population per year. It seems certain that many cases of slight unrecognized infection also occur, and it is probable that, as in other communicable diseases, these mild and missed cases contribute to the spread of the infection. In cities, therefore, it might be expected that many adults would have an acquired immunity and that the number of immune adults would be proportionally more than in childhood. The figures of Park⁵ in New York (33 per cent.), Kolmer⁶ in Philadelphia (35 per cent.), Bundesen⁷ in Chicago (33 per cent.), Moody⁸ in St. Louis (27 per cent.), and Leete⁹ in Edinburgh (34 per cent.) indicate that such is the case. In smaller communities, such as villages, towns and even the smaller cities, on the other hand, diphtheria is not prevalent, and many such communities are free from the disease for long periods, although the occasional epidemics which occur show a higher mortality than in cities. Extensive statistical studies on diphtheria immunity, as shown by the Schick test in these smaller communities, are not available, but it is significant that Lilly¹⁰ found 57.6 per cent. of positive reactions

3. Hull, H.: Diphtheria from the Public Health Standpoint, Penn. M. J. **23**:638 (Aug.) 1920.

4. Zingher, A.: Diphtheria Preventive Work in the Public Schools of New York City, Arch. Pediat. **38**:336 (June) 1921.

5. Park, W. H.; Zingher, A., and Serota, M. H.: The Schick Reaction and Its Practical Applications, Arch. Pediat. **31**:481 (July) 1914.

6. Kolmer, J. A., and Moshage, E. L.: The Schick Reaction for Immunity in Diphtheria, Am. J. Dis. Child. **9**:189 (March) 1915.

7. Bundesen, H. N.: Schick Reaction with a Report of 800 Tests, J. A. M. A. **64**:1203 (April 10) 1915.

8. Moody, E. E.: The Intradermic Diphtheria Toxin Test, J. A. M. A. **64**:1206 (April 10) 1915.

9. Leete, H. M.: The Schick Reaction, Lancet **1**:192 (Jan. 24) 1920.

10. Lilly, T. E.: An Experience with the Schick Test and Toxin-Antitoxin, and a Plea for Their Use in the Extinction of Diphtheria, Boston M. & S. J. **182**:110 (Jan. 29) 1920.

in 257 boys from 15 to 21 years old in the Industrial Home for Boys at Shirley, Mass. Tests made on a number of students in the Washington University Medical School, two-thirds of whom come from smaller towns, show a similar high percentage of positive Schick reactions. More recently Garland¹¹ has found that of 380 nurses tested in a number of Massachusetts hospitals 52.8 per cent. gave positive Schick reactions.

The effect of the toxin-antitoxin injections on the Schick reaction is shown in Tables 1 and 2. Not all the nurses who gave positive reactions are included since some left training, and a group of army nurses were not immunized because they did not have duty on the diphtheria

TABLE 1.—EFFECT OF FIRST SERIES OF TOXIN-ANTITOXIN INJECTIONS ON SIXTY-TWO NURSES WITH POSITIVE SCHICK REACTIONS

	62									
Before toxin-antitoxin	27++			27+			8±			
4 months later	1++	6+	1±	19—	4+	1±	22—	2±	6—	
From 9 to 15 months later	1++	4+	2—	1±	2+	2*	1±	1±	1*	

* Not retested.

TABLE 2.—EFFECT OF A SECOND SERIES OF TOXIN-ANTITOXIN INJECTIONS ON EIGHT NURSES WHO WERE NOT IMMUNIZED BY THE FIRST SERIES

	8					
Before second series.....	1++		4+		3±	
From 4 to 8 months later	1—	2+	1±	1—	2±	1—

wards. In all sixty-two nurses have been given the toxin-antitoxin, and when retested from four to six months later, forty-seven, or 75.8 per cent., were immune. Two more gave negative reactions nine and fifteen months after the injections, bringing the total number immunized to 79 per cent. Of the remaining thirteen, five had graduated or had left training before further tests could be performed, but the remaining eight were given a second series of three toxin-antitoxin injections (Table 2). Only three of these gave negative reactions when

11. Garland, J.: Report on the Recent "Schick Test" Campaign, Boston M. & S. J. **185**:432 (Oct. 13) 1921.

tested later. Since in a certain number of instances the immunity is late in developing it is not certain whether these three negative reactions resulted from the first series of injections or from the second. Certainly a few individuals appear definitely refractive to immunization as indicated by the Schick test.

The effect of the immunization on the incidence of clinical diphtheria in the group of nurses studied is especially striking and is shown in Table 3.

It will be noted that twenty nurses, or 28.6 per cent. of those on duty in the contagious pavilion, developed diphtheria during the three years preceding the immunization, while only two in the group (1.5 per cent.) contracted the disease in a four years' period after the immunization was started. One of the latter was assigned to duty on the diphtheria ward through an error just after her first dose of toxin-antitoxin,

TABLE 3.—EFFECT OF IMMUNIZATION ON DIPHTHERIA MORBIDITY IN NURSES

	Before Immunization of Nurses			After Immunization of Nurses			
	1915	1916	1917	1918	1919	1920	1921
Cases of diphtheria reported in St. Louis	3,389	3,114	3,339	2,015	3,976	4,660	3,561
Cases of diphtheria and diphtheria carriers treated in the St. Louis Children's Hospital	110	69	37	70	126	110	132
Total nurses in Washington University Training School	73	85	92	110	80	99	106
Washington University nurses on contagious service	20	32	18	32	35	31	32
Washington University nurses with diphtheria	7	9	4	0	1*	1†	0
Total affiliated nurses (not immunized)	24	20	24	25	14	19	31
Affiliated nurses with diphtheria (not immunized)	2	1	0	2	0	1	4

* Nonimmune on duty in diphtheria ward by mistake.

† Diagnosis uncertain.

and two days later developed clinical diphtheria. In the other instance, a nurse who had been immunized and had a negative Schick reaction one year previously, developed a slightly red throat which was painted with a strong silver nitrate solution. Cultures taken were positive for diphtheria bacilli and a grayish exudate developed on both tonsils. It was thought wiser to administer antitoxin and she recovered promptly. Cultures remained positive for more than a month. It could not be decided definitely whether the exudate was diphtheritic or the result of the superficial necrosis from the silver nitrate application in a nurse who was a diphtheria carrier. A Schick test done six months after the illness was negative, so that the latter assumption is probable.

More cases of diphtheria were treated in the wards during the period after immunization than during the previous three years, and the morbidity in the city was also slightly higher during this latter period. As controls may be taken the group of nurses from several affiliated

institutions who spent three months in the Children's Hospital, part of the time in the contagious pavilion. No skin tests or immunity studies were made on this group. Their contact with patients was the same as that of the nurses of the Washington University Training School except that they spent only about half the time on duty in the contagious disease wards. In each of the three-year periods, 1915-1917 and 1918-1920, three nurses from this group contracted diphtheria and four more during 1921. It might be mentioned, also, that during the latter period in which the Training School Nurses were immunized, two interns and four of the maids and office help in the Children's Hospital developed clinical diphtheria.

The effect of immunization by toxin-antitoxin on this group of adults was of particular interest on account of the fact that all were exposed to diphtheria during their training. That a considerable proportion was susceptible to the infection is shown by the rather high morbidity in the group during the control period of three years before immunization was instituted. During this time 28.5 per cent. of the nurses in the contagious pavilion developed clinical diphtheria. This must be regarded as a minimum since probably all were not exposed to the infection equally. For example, certain nurses were probably detailed to scarlet fever, or measles wards for a considerable portion of their service and may have spent only a few days on the diphtheria ward. The actual intimate exposure to diphtheria cases, therefore, varied with the number of cases of other communicable disease which happened to be treated in the hospital. The number of susceptible individuals during the first three years' period as indicated by those having clinical diphtheria is consequently not absolutely comparable to the susceptibles of the second four years' period as indicated by the Schick test. However the individual exposure may have varied during the two periods, the group exposure during these periods can be compared and it will be noted that almost double the number of patients with diphtheria were cared for by the immunized group than by the control group. The almost perfect protection from infection by the immunization is, therefore, more striking.

The number of individuals in whom the Schick reaction remained positive after three doses of toxin-antitoxin is somewhat larger than is usually reported in children after immunization. Even after a second series of injections five out of a group of eight were persistently positive. All these nurses have completed their service in the contagious pavilion and none has developed diphtheria. In such a small number no conclusion regarding immunity is possible. It would seem that if a negative Schick reaction does not follow three injections of toxin-antitoxin, further injections are also likely to fail in suppressing the reaction.

SUMMARY

The Schick test was positive in a group of adults (nurses) in 58.5 per cent. It is suggested that this high proportion of nonimmunes may be related to the fact that most of the individuals in the group were reared in smaller communities where contact with diphtheria is less than in cities.

During a four years' period all nurses with positive Schick reactions were given injections of toxin-antitoxin, and as a result more than 80 per cent. were immunized. In a small number the Schick reaction remained positive after two series of toxin-antitoxin injections.

As a result of the immunization, there was a decrease in the incidence of clinical diphtheria among these nurses of at least 90 per cent. as compared to a previous three years' period.

It is relatively easy to protect an entire nursing staff from contracting diphtheria by the use of the Schick test and toxin-antitoxin injections, and this procedure should be carried out in all institutions caring for children.

I wish to thank the staff of the Washington University School of Nursing for assisting in this study, and especially Miss Minnola Stallings, whose interest and cooperation have greatly facilitated the work.

THE ASPIRATION OF STEARATE OF ZINC IN INFANCY

A CLINICAL AND EXPERIMENTAL STUDY *

HENRY HEIMAN, M.D. AND PAUL W. ASCHNER, M.D.

NEW YORK CITY

During the past few years stearate of zinc has largely replaced talcum as a dusting powder in the nursery. With its ever widening use there has developed a striking increase in the number of disastrous results in infants from its accidental aspiration.

We thought it might be worth while to present a clinical study of twelve cases observed by one of us (Heiman) and the results of experiments with zinc stearate insufflation in animals (Aschner). The cases were observed in private practice and in the Children's Wards of Mt. Sinai Hospital.

To understand the mode of aspiration one must be familiar with the powder as prepared for use in the nursery. It is packed in a cylindrical box having large perforations at one end in order to "shake out" the powder. Usually a sliding cover is provided. The perforations are made unusually large because of the tenacious quality of zinc stearate. The infant takes hold of the box, as it does its nursing bottle, and draws it quickly toward the face. If the sliding cover has been left open, there is a sudden shower of a large mass of powder, which partially or wholly asphyxiates the infant. Some of the powder is thus aspirated into the bronchi and lungs.

The onset of trouble is sudden and stormy, with rapid respirations and cyanosis. Complete asphyxia may occur. One of our patients died within twenty-four hours after the accident. The infant, aged 8 months, was given a box of zinc stearate to play with. The powder spilled on the child's face producing an asphyxia with marked dyspnea and cyanosis. At the hospital the Auer-Meltzer apparatus, as well as hypodermic stimulation were employed without avail. Physical examination of the lungs revealed the diffuse fine crepitating râles of an extensive bronchopneumonia. Postmortem examination (macroscopically) showed small areas of consolidation on the posterior aspect of both lungs.

All of the cases, however, are not of this fulminating type. Three infants developed signs of bronchopneumonia with symptoms of an

* Received for publication Jan. 9, 1922.

* From the Pediatric Service and the Pathological Laboratory of Mt. Sinai Hospital.

acute toxemia, which lasted from two to three weeks. The temperature was intermittent, varying from 99 to 105 F. Respirations were rapid in all these cases, in one case 90 per minute. Cyanosis was marked at the onset. The pulse was rapid. Abdominal distension was marked in two cases. Recovery was gradual by lysis during the third week. The treatment is that of bronchopneumonia. Hygienic care and efficient nursing are of prime importance. An abundance of fresh air

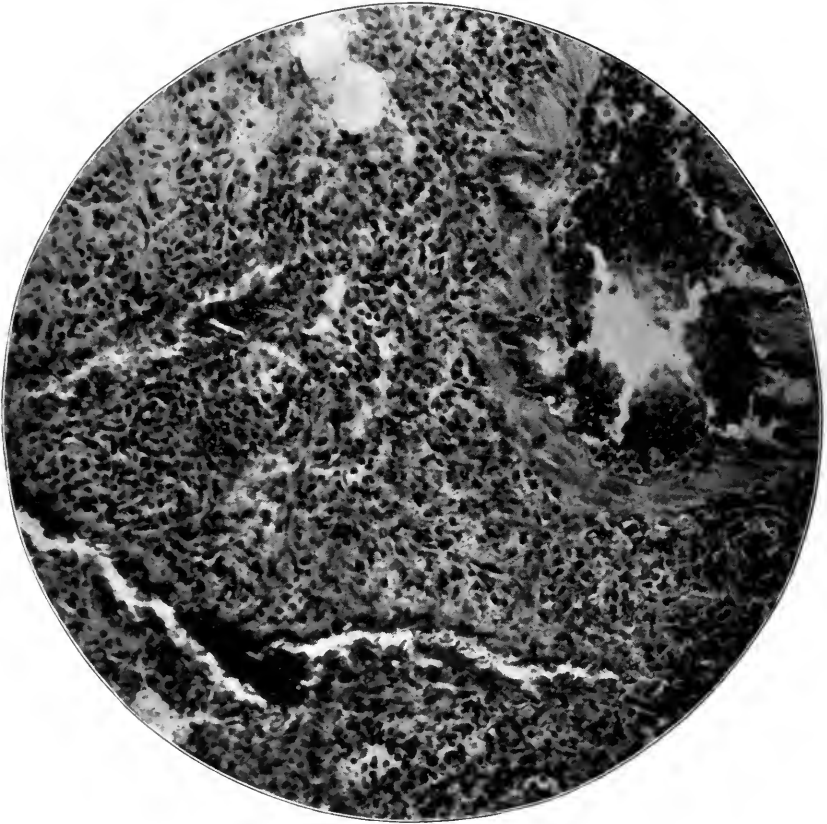


Fig. 1.—Proliferation of bronchial epithelium. Bronchopneumonia. X260.

and sunlight are essential. Diluted milk, gruels, fruit juices and water should form the chief elements of food. To provide proper elimination *magma magnesiæ* in the morning and an enema should be given each night. Hydrotherapy in the form of warm packs between 80 and 90 F. and stimulation may be necessary.

In eight of our cases the initial partial asphyxia was followed by a gradual recovery without definite involvement of the lungs. The rapid respirations and cyanosis which followed immediately on the

inhalation of the powder subsided during the course of three days. The temperature was only slightly elevated.

The stearate of zinc container as now prepared for the nursery is a distinct menace to the health of infants. May we not enlist the efforts of the medical profession to eliminate this dangerous type of container from the nursery?

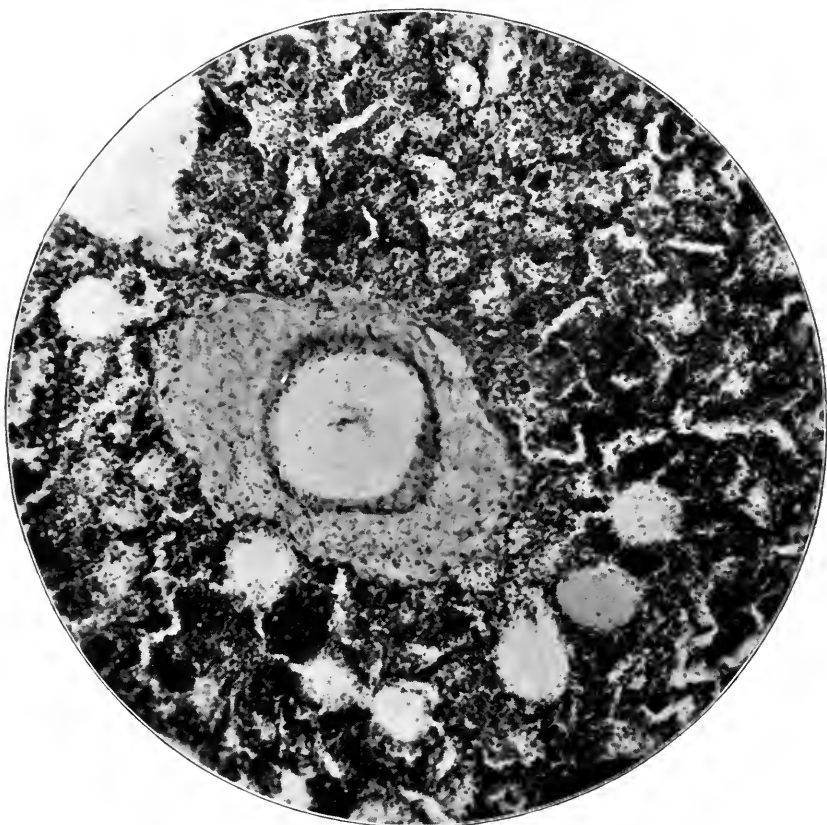


Fig. 2.—Hemorrhagic area. Perivascular edema. X170.

NECROPSY REPORT

The patient was 8 months old. There were no evidences of pleuritis. The lungs were salmon pink in color, air containing, with no extensive consolidation. Along the posterior borders were a few darker firmer areas. Microscopic sections showed intense congestion with areas of interstitial round cell infiltration. The bronchioles showed round and polymorphonuclear leukocytic infiltration of their walls.

Efforts to induce dogs to inhale zinc stearate in a manner similar to that which occurred in the clinical cases were unsuccessful. The

method used by Lamar and Meltzer¹ in their experimental production of pneumonia was therefore resorted to with slight modification. The animal was etherized. A sterile rubber tube, 1 cm. in diameter, was passed just beyond the vocal cords. Sterile zinc stearate was then insufflated through the tube with a DeVilbiss powder blower. Samples of the powder from our cases had proved sterile with only one exception in which a gram-positive saprophytic bacillus was found.

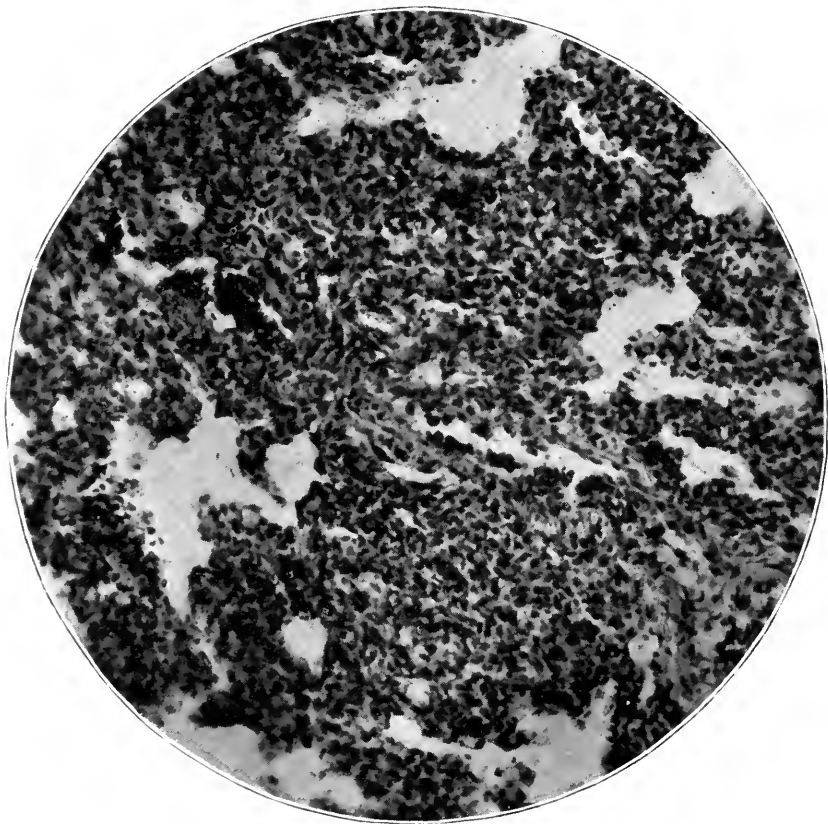


Fig. 3.—Interstitial pneumonitis. X260.

The bulb was squeezed four or five times, the tube was pinched a few seconds, and then withdrawn. Anesthesia was maintained for another five minutes.

The dogs appeared ill for a few days with loss of appetite and temperature of 101 to 103 F. Some dogs developed a dry brassy cough. Difficulty in breathing was of short duration. A few dogs

1. Lamar, R. V., and Meltzer, S. J.: *J. Exper. M.* **15**:133, 1912. Wollstein, M., and Meltzer, S. J.: *J. Exper. M.* **16**:126, 1912; **17**:353, 1913; **18**:543, 548, 1913.

showed practically no symptoms. Three dogs were killed three days after insufflation, two dogs after five days, and one dog ten days after. One dog was insufflated twice, another four times. The lesions produced can best be described by the following protocols.

Experiment 1.—Dog killed three days after zinc stearate insufflation. Lungs well aerated, very pink. Some small raised whitish areas in lower and middle lobes. Microscopic sections show congestion and increase of interstitial

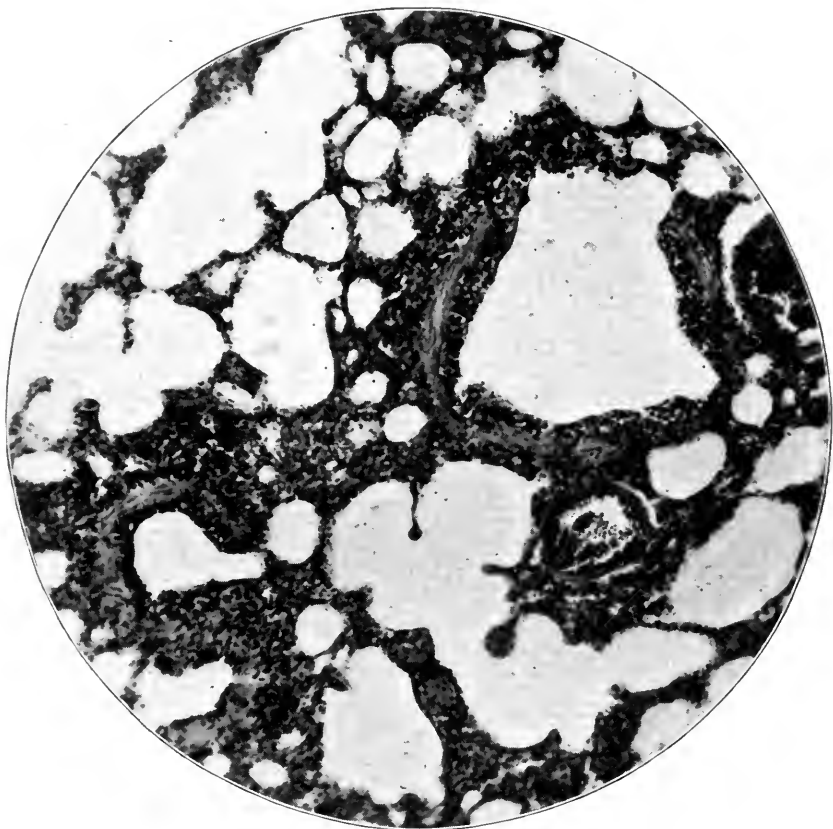


Fig. 4.—Slight interstitial pneumonitis after talcum insufflation. X170.

tissue especially in vicinity of the bronchioles. Vessels show perivascular edema, and in places round cell infiltration of their walls. Bronchioles show epithelial proliferation with some formation of polypoid excrescences. The lumen of some bronchioles contains amorphous detritus and round cells. The outer coats present round and polymorphonuclear cell infiltration with deposit of pigment. Parenchyma about bronchioles shows areas of alveolar desquamation with pigment in many of the desquamated cells. The picture is that of a catarrhal or bronchopneumonia (Fig. 1).

Experiment 2.—Dog killed three days after zinc stearate insufflation. Microscopic sections show interstitial pneumonitis and peribronchitis. There

are also areas of intense congestion and hemorrhage. Some of the vessels show edema, some contain thrombi (Fig. 2).

Experiment 3.—Dog killed five days after zinc stearate insufflation. Lungs very pink. The right lower lobe appears poorly aerated and feels heavy. Sections show widespread interstitial pneumonitis. Alveoli are reduced in size by a highly vascular connective tissue interstitium. The vestibulae appear numerous and prominent. Larger air passages show areas of submucous round cell infiltration (Fig. 3).

Similar lesions were obtained in all the experiments.

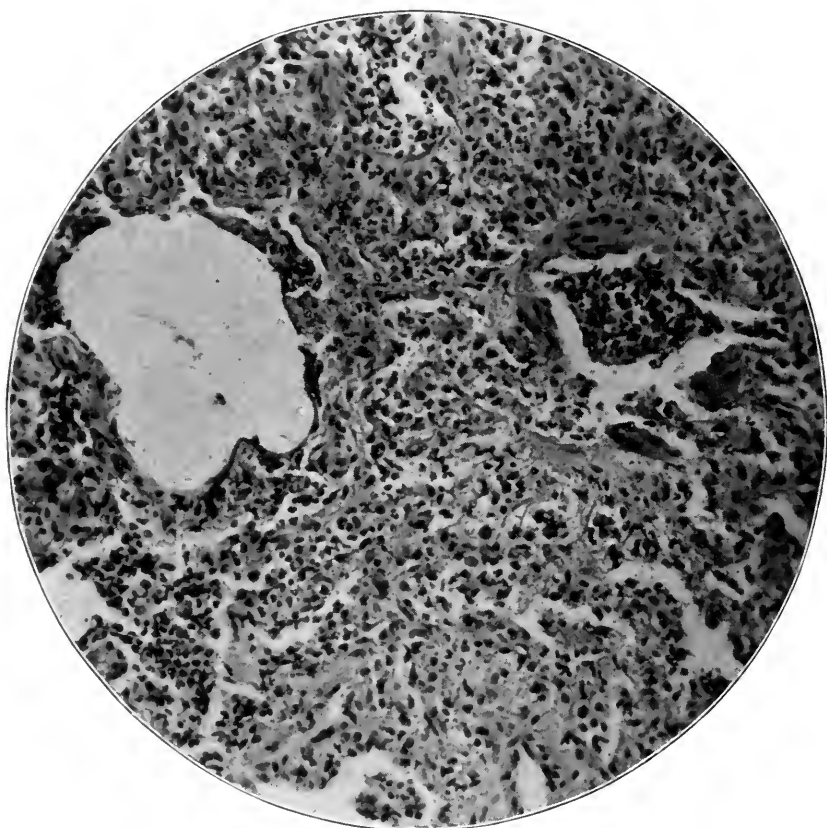


Fig. 5.—Area of more recent polymorphonuclear cell infiltration of parenchyma. X260.

For purposes of comparison two dogs were insufflated with sterile talcum powder with the following results:

Experiment 4.—Dog killed three days after talcum insufflation. No gross changes. Sections show few small scattered areas of peribronchial infiltration with round cells. No intrabronchial exudation, no changes in bronchial or alveolar membranes.

Experiment 5.—Dog killed five days after talcum insufflation. No gross changes. Sections show a rather diffuse but slight increase of interstitial

tissue with small round cell foci. There are round cell foci in walls of some larger bronchi and about the larger vessels (Fig. 4).

The lesions produced by talcum powder are similar in kind but lesser in degree than those produced by zinc stearate. It is probable that the physical properties of the talcum permit the animal to expel a good deal of the foreign material. Zinc stearate is, on the contrary, an extremely tenacious powder.

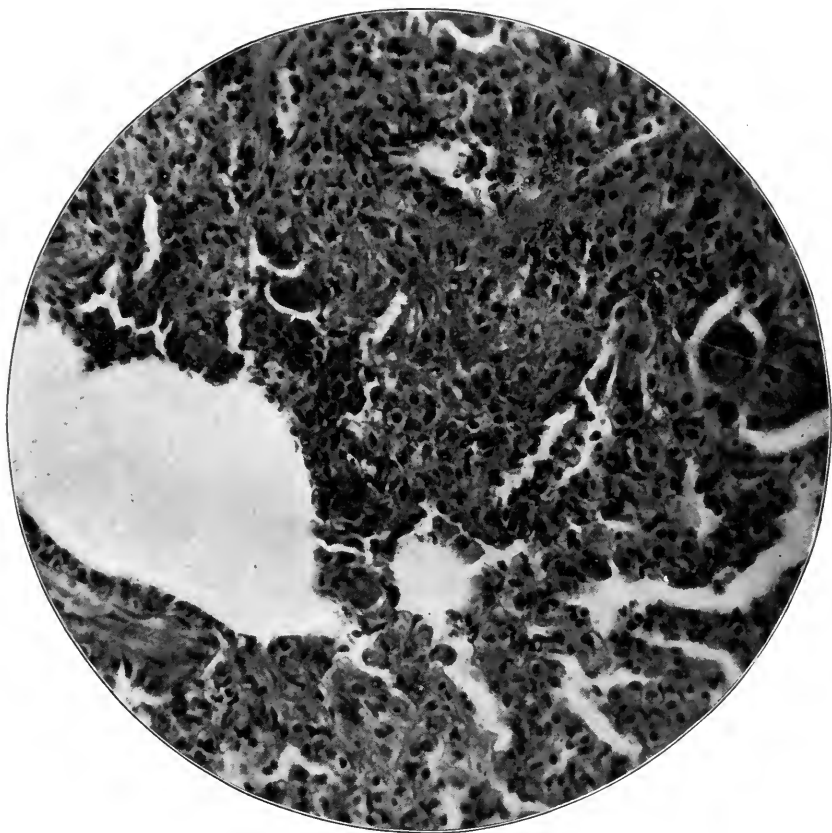


Fig. 6.—Area of older organizing pneumonitis. X260.

Cultures of the lung tissue were made in three instances and proved sterile in each.

It is of interest to note that Meltzer and Kline² insufflated unorganized substances and produced pneumonic lesions. Aleuronat and starch produced lesions similar to those obtained after insufflation of virulent pneumococci. Egg yolk and lecithin produced lesions resem-

2. Meltzer, S. J., and Kline, B. S.: *Proc. Soc. Exper. Biol. & Med.* **13**:29, 1915.

bling those of avirulent pneumococci and *B. megatherium*. Lung cultures in these experiments proved sterile.

Repeated insufflation of zinc stearate at intervals of about a week were carried out in one experiment.

Experiment 6.—Dog killed two days after last of four insufflations. Lungs white with some gelatinous areas along free margins. Bronchioles, some occluded by a hyaline material containing epithelial and round cells, peribronchial infiltration with round and polymorphonuclear cells. Adjoining areas of interstitial pneumonitis and alveolar desquamation. An extensive organizing fibrotic process is seen in the parenchyma (Figs. 5 and 6).

The production of a fibrosis of the parenchyma by repeated insufflation of zinc stearate may explain the beneficial results noted by Lynah³ in cases of bronchiectasis and lung abscess after injections of bismuth mixtures by means of the bronchoscope. The bismuth is retained in the tissues for days after the procedure and probably induces an organizing process in the lung about the site of injection.

The authors wish to acknowledge their indebtedness to Dr. Jerome Ziegler for valuable aid in the animal experiments and to Dr. F. S. Mandlebaum, director of laboratories, for the microphotographs.

3. Lynah, H. L., and Stewart, W. H.: Ann. Surg. **73**:362, 1921.

HEALING OF HYPERTROPHIC PYLORIC STENOSIS AFTER THE FREDET-RAMMSTEDT OPERATION *

MARTHA WOLLSTEIN, M.D.

NEW YORK

The following study is based on the gross and microscopic examination of the stomachs of twenty-five infants who came to necropsy with hypertrophic pyloric stenosis. Two children of the series died before operation, and the rest succumbed from twenty-four hours to two years after the Fredet-Rammstedt operation had been performed. The age of these children, at necropsy, ranged from 4 weeks to 2 years.

PATHOLOGY

The stomachs with hypertrophied pylorus, when observed before or soon after operation, were dilated and often twice the size of the normal stomach of the same age. The pylorus measured from 1.5 to 3 cm. in length as compared with the normal length of from 1 to 1.5 cm.. The feel of the pylorus was abnormally thick and hard.

On opening the stomach it was usually empty of food, but it always contained a large amount of mucus, with a thick plug in the pyloric opening. The mucosa showed nothing abnormal. The thickening of the pylorus was due to an increase in the width of the circular muscle coat, the other layers showing no change from the normal. In a few cases the wall at the pyloric end of the stomach was slightly thicker than usual, but at the cardiac end it was always normal. The measurements of the circular muscle coat of the hypertrophied pylorus compared with those of the normal pylorus in infants from 1 to 3 months old are given in the accompanying table.

It will be seen that in the hypertrophied pylorus the circular muscle was from 3 to 7 mm. thick, thirteen out of twenty cases measuring 4 mm. or more. The normal stomachs, on the other hand, showed a pyloric circular coat between 0.5 and 2.5 mm. in thickness, and seventeen measured 2 mm. or less. The contrast is marked. The normal thickness of the pyloric circular muscle coat in children under 3 months of age may be given as not greater than 2.5 mm., the average being 1.6 mm. The hypertrophic pylorus at this age, on the other hand, shows a circular muscle layer of from 3 to 7 mm. in thickness, the average being 4.4 mm.

MICROSCOPIC ANATOMY

On microscopic examination it was found that the changes were limited to the submucosa and the circular muscle coat. The mucosa

* Received for publication, Jan. 21, 1922.

* From the Laboratory of the Babies' Hospital.

was practically unchanged in every instance. The absence of any evidence of inflammatory lesion from this coat would seem to place the vomiting entirely in the mechanical category, due to over distension of the stomach because of the tightly closed pylorus. The submucosa was often edematous and thus apparently wider than usual. The characteristic change was seen in the circular muscle coat, which was at least twice and often three times thicker than normal. The thickness was due simply to a larger amount of muscle tissue in the circular coat, while the connective tissue between the muscle cells was not increased. In no case of my series had there been any fibrous con-

THICKNESS OF CIRCULAR MUSCLE COAT OF PYLORUS

Age Weeks	Normal Pylorus Mm.	Hypertrophic Pyloric Stenosis Mm.
4½.....	0.0025, 0.0005	0.0035
5.....	0.0021, 0.0015, 0.002	0.005, 0.006, 0.004, 0.007, 0.004
6.....	0.001, 0.0015, 0.0015	0.0035, 0.0035, 0.004
7.....	0.001, 0.00125	0.005, 0.0035
8.....	0.002, 0.00125	0.005, 0.003, 0.004
9.....	0.001, 0.002,	0.0045, 0.004,
10.....	0.001, 0.002	0.0045
10.....	0.002, 0.0015	0.0045, 0.0035
12.....	0.001, 0.0025	0.006,

nective tissue thickening. This fact was well demonstrated by staining the sections for connective tissue with Van Gieson's stain (Figs. 1 and 2). The hardness and firmness apparent on palpating the pylorus is due only to the thick and firmly contracted muscular ring. The serosa was normal when the specimen had been obtained before operation or after the healing of the operation wound. Edema was not present at either of these periods.

HEALING

The healing after the Fredet-Rammstedt operation, which consists simply in incising the serous and muscle coats of the pylorus down to the submucosa, is an interesting process, best illustrated by pictures of sections made from the stomachs at various periods after operation. My series includes sections from cases in which death occurred in twenty-four hours, four days, nine days, ten days, thirteen days, twenty-five days, six weeks, sixteen months and two years after operation. In twenty-four hours intense congestion of the blood vessels of all the coats along the line of incision, some edema of all the coats and hemorrhage into the submucosa were present. There was a wide gap between the cut ends of the muscle coats, over which lay a delicate layer of fibrin with few polymorphonuclear cells. The submucosa showed a similar cellular infiltration, more marked in some cases than in others.

In four days (Fig. 3), there was a small plug of fibrin in the base of the gap between the incised edges of the wound, and the connective

tissue of the serous coat had almost covered the cut ends of the muscle by proliferation of its cells, between which thin walled blood vessels were seen. The most superficial connective tissue cells had become flattened into a protective layer like endothelium over this delicate granulation tissue. Since we know that unstriated muscle cells regenerate only to a minimum degree, if at all, it remains for the connective

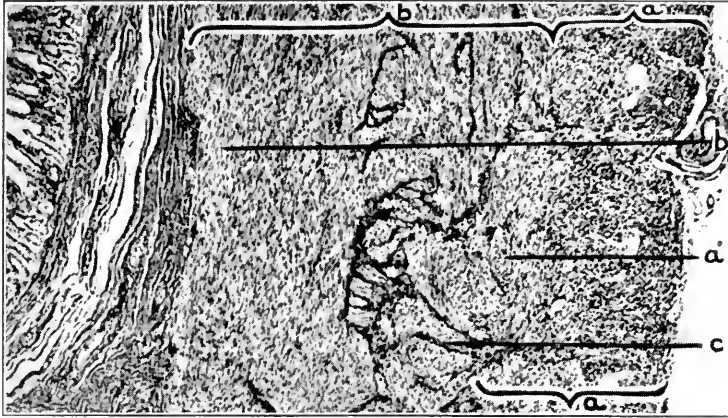


Fig. 1.—Normal pylorus: (a) longitudinal muscle coat; (b) circular muscle coat; (c) fibrous connective tissue.

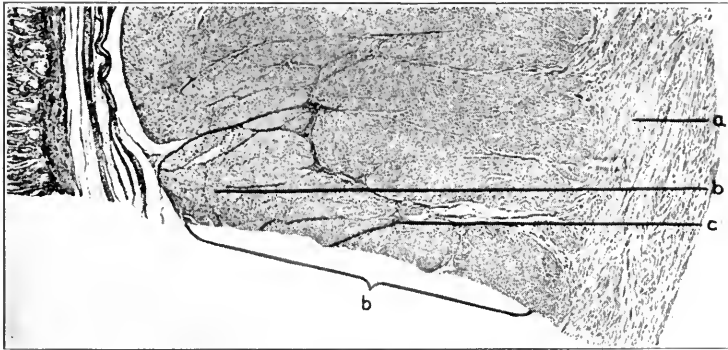


Fig. 2.—Hypertrophied pylorus: (a) longitudinal muscle; (b) circular muscle coat; (c) fibrous connective tissue. Note hypertrophied circular muscle and no increase in connective tissue.

tissue of the serosa and submucosa to fill in the gap between the edges of the operation wound. This proceeds as indicated above, and the muscle cells show no attempt at proliferation.

In nine days and ten days after operation (Fig. 4) the gap between the edges of the wound is still wide but the entire length of the incision

is covered with a delicate layer of cellular, fibrous connective tissue, which represents the proliferated serous coat, and touches the submucosa at the base of the incision. The cut ends of the muscle layers are still wide apart, and consequently there is a depression on the outer surface of the pylorus at the site of operation. At this time, however,

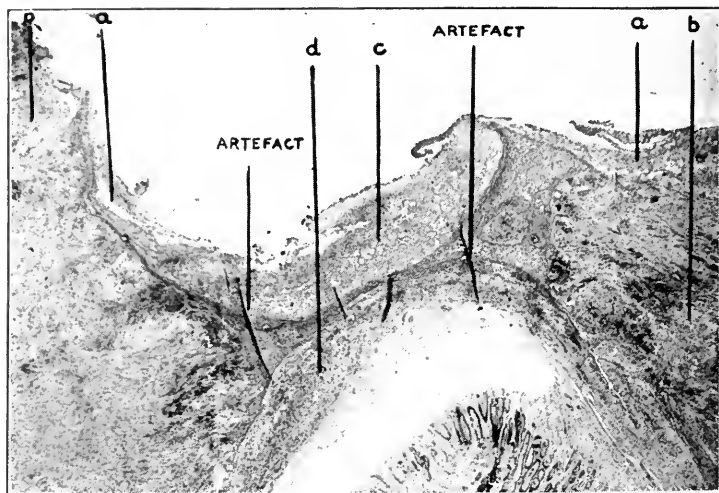


Fig. 3.—Four days after Fredet-Rammstedt operation. (a) Layer of delicate granulation tissue over edges of incised muscle (b) and in base of wound (c) close to submucosa (d) which shows cellular infiltration.

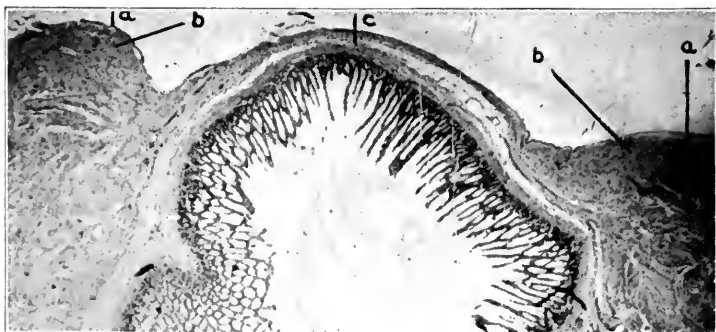


Fig. 4.—Ten days after operation. Wound healed. (a) Edges covered by thin layer of connective tissue. (b) Wide gap between cut ends of muscle coat. (c) Submucosa and serosa in contact.

as Dr. Downes has pointed out, the pylorus feels softer than at the time of operation.

As the muscle coat relaxes from gradual lack of obstruction and consequent cessation of overstimulation of its contractile power, and

the newly formed connective tissue, thin as it is, contracts, as all connective tissue tends to do, the two divided ends of the muscle coats tend to approach each other and the space between them becomes less and less. Twenty-five days after operation there is only a narrow scar at the site of the incision in the pylorus, and no longer a depression at this point. Microscopically there is a thin layer of fibrous connective

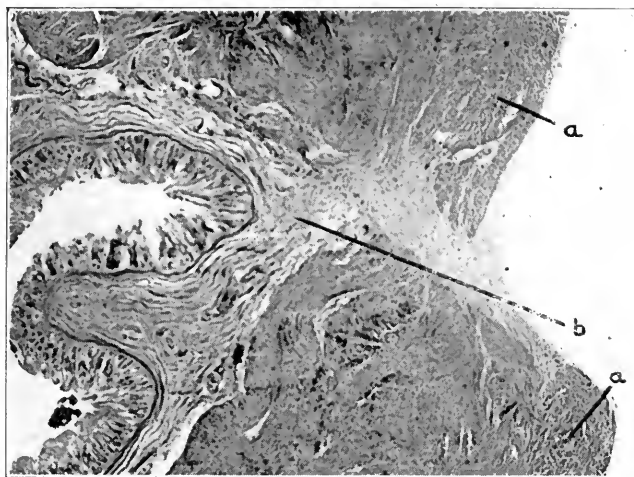


Fig. 5.—Twenty-six days after operation. (a) Ends of muscle coat drawn close together and layer of fibrous connective tissue between them. (b) This connective tissue is continuous with the connective tissue of both submucosa and serosa.

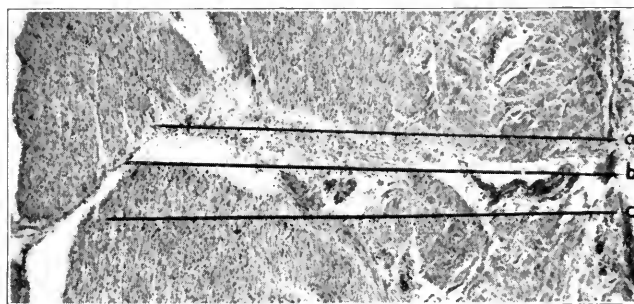


Fig. 6.—Two years after operation. (a) Ends of muscle coats almost in contact. (b) Very thin layer of fibrous connective tissue between them.

tissue between the ends of the muscle coats (Fig. 5). This fibrous tissue is continuous with the submucosa above and the serosa below. At this stage the stomach is normal in size and not distended, while the pylorus feels but little more firm than normal.

The final stage is illustrated by the sections made from a stomach removed at necropsy two years after operation (Fig. 6). The stomach

of this child, who died of aortic stenosis, was 12 cm. long, and the pylorus did not feel abnormally firm. The gastrohepatic omentum was only 1.5 cm. long and very thick. On the under surface of the pylorus, near the greater stomach curvature, there was an irregularly quadrangular area 5 by 4 mm., over which the peritoneum was thickened, but there was no depression. The pyloric circular muscle was 3 cm. thick and the mucosa was normal. On microscopic examination the end result of the healing was seen in an almost complete approximation of the cut ends of the muscle coats with a thin line of connective tissue between them.

DISCUSSION

The healing of the wound in the pylorus made by the Fredet-Rammstedt operation is brought about by the connective tissue of the serous and submucous coats of the stomach. The unstriped muscle cells of the cut muscle layers take no active part in the healing process, as evidenced by the absence of division among these cells. The raw, cut muscle edges and the exposed layer of submucosa which protrudes into the gap between them become covered by a thin layer of delicate granulation tissue, which, by the ninth day, has become cellular fibrous connective tissue. By the contraction of this layer of fibrous connective tissue and the relaxation of the unstriped muscle, the edges of the wound are gradually brought into contact and the pylorus relaxes. In from nine to thirteen days after operation the wound has healed completely, though the site of operation still shows a very evident depression. In twenty-five days this depression has become gradually less, and in six weeks only a delicate scar remains. In sixteen months a very thin linear scar was present. In two years the scar was scarcely visible. Within two weeks after operation the pylorus feels softer than it had felt at operation, and in twenty-five days the stomach is normal in size and the pylorus but slightly firmer than normal. This is in contrast with the condition of the pylorus after gastro-enterostomy, where Dr. Holt¹ found it quite unchanged in thickness from six months to two years after operation.

SUMMARY

It has been shown that the lesion in hypertrophic pyloric stenosis is a hyperplasia of the unstriped muscle cells of the circular coat, while the connective tissue is not increased.

After the Fredet-Rammstedt operation healing is brought about by the cells of the serosa and submucosa, but the unstriped muscle cells take no part in the process.

The wound in the pylorus is healed within nine days. The pylorus has become relaxed within two weeks. The stomach has returned to

1. Holt, L. Emmett: *J. A. M. A.* **68**:1517 (May 26) 1917.

its normal size within a month and the gap between the cut ends of the muscle coats has practically disappeared in six weeks. In two years only a thin line of connective tissue fibers separates these two muscle ends, and the stomach is quite normal.

In contrast to the operation of gastro-enterostomy which leaves the pylorus unchanged, the Fredet-Rammstedt operation cures the pyloric lesion.

The cases in this series came from the medical service of Dr. Holt and from the surgical service of Dr. Downes, to both of whom I am indebted for the use of the material.

THE VITAMIN REQUIREMENT OF VARIOUS SPECIES OF ANIMALS

III. THE PRODUCTION AND CURE OF XEROPHTHALMIA IN THE SUCKLING

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AND

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It is a well known fact that vitamin A is necessary in the diet if normal growth and reproduction shall take place. In the absence of this particular dietary factor a condition known as xerophthalmia or keratomalacia results. It is equally well known that the higher animals cannot synthesize this vitamin and that they must depend, therefore, on green plant tissue as the ultimate source of the vitamin. During the past year some work has been done demonstrating that the quantity of this vitamin in milk will vary with the quantity of vitamin A in the diet.¹ This is to be expected since the animal cannot synthesize this unknown substance, and consequently if the vitamin is not present in the diet the mother cannot secrete it into the milk.

Andrews² showed that the milk of a mother whose children had died from beriberi, and whose diet was, therefore, presumably deficient in vitamin B, produced polyneuritis in suckling pups. It must be remembered, however, in this connection that the pups were fed a milk which was not normal for the species, and it may well be that the requirement of pups for vitamin B is different than that of man. We have some data on this point which will form a separate paper of this series.

McCollum³ has shown that mother rats which were kept on a satisfactory diet until the birth of the young and then were at once restricted to diets lacking vitamin A did not rear the young. He believed it probable that this milk was deficient in quality rather than quantity. He also reported the occurrence of sore eyes in young rats on diets deficient in vitamin A. These sore eyes, however, often occurred after the suckling period, when the young were consuming some of the mother's diet. He also noticed sore eyes on a ration

* Received for publication, Feb. 24, 1922.

* From the Department of Chemistry and the Agricultural Experiment Station, Iowa State College.

1. Drummond, Coward and Watson: *Biochem. J.* **15**:540, 1921.

2. Andrews: *Philippine J. Sc., Ser. B* **7**:67, 1912.

3. McCollum and Simmonds: *Am. J. Physiol.* **46**:275, 1918; McCollum, Simmonds and Pitz: *J. Biol. Chem.* **27**:33, 1916.

which contained 5 per cent. butter fat, but was deficient in other respects. We have noticed similar symptoms in both rats and rabbits on defective diets, which symptoms could not be relieved by the administration of butterfat. In a few cases the animals became totally blind. McCollum did not attempt to cure this condition by feeding vitamin A to the mother. In his experiments the mother rats no doubt had, at the beginning of the suckling period, considerable reserve of vitamin A in their tissues since they had been upon an adequate diet up until the young were born.

In a previous article we ⁴ have demonstrated that the rabbit requires more vitamin A than the rat for normal growth and reproduction. The rabbit consistently develops xerophthalmia on diets deficient in vitamin A.⁵ This symptom, however, is not to be confused with the occasional occurrence of sore eyes under other unfavorable conditions of environment and diet even though vitamin A is present in the diet. This latter type of sore eyes is probably due to direct infection.

It is possible to feed a rabbit a diet which is below the optimum in its vitamin A content which will produce slow growth with no apparent symptom of dietary deficiency. This kind of diet was fed to six rabbits, five males and one female. The diet had the following composition:

White corn.....	55
Linseed oil meal.....	22
Oats	15
Meat meal tankage.....	5
Supplementary salt mixture.....	3
	<hr/>
	100

This diet has been reported ³ as deficient in vitamin A and capable of producing xerophthalmia in young growing rabbits. The animals mentioned were started on this diet, however, at a weight of 2,000 gm. and were three-fourths grown. After a period of three months they reached an average weight of 2,400 gm. and appeared to be in excellent condition. They were healthy, fat, clear of eye and possessed sleek, fine coats. At this time the female gave birth to five young which she suckled and cared for in a normal manner. Soon after the birth of the young the mother began to lose in weight and developed symptoms of xerophthalmia. Two of the young died before their eyes were opened. The rabbit normally opens its eyes at the age of 10 days. About one week later a third young rabbit died with typical symptoms of xerophthalmia. The two remaining young, which were more vigorous, remained alive with distinct evidence of xerophthalmia. At this point the mother was given in addition to her ration from 1 to 2 gm. butter fat per day. The xerophthalmia in the mother

4. Nelson, Lamb and Heller: *Am. J. Physiol.* **59**:335, 1922.

5. Nelson and Lamb: *Am. J. Physiol.* **51**:530, 1920.

cleared up slowly. One of the young (the black shown in the photograph with eyes swollen shut) had become very weak, and died three days later, although the eyes were considerably improved. The other young (grey shown in picture with its eyes almost swollen shut) showed marked improvement in the eye condition and began to grow very rapidly, doubling its weight in thirteen days thereafter. The two young were in very poor condition, had ceased growing entirely, and if butter fat had not been fed to the mother we believe they would certainly have died within twenty-four hours. It seems quite evident that the mother immediately transferred the vitamin A in the butter fat to her own milk and thereby relieved the offspring. During all this time the young were suckling the mother and eating no other food.



The effect of the strain of reproduction on the development of xerophthalmia. The grown rabbit on the left is normal. The doe on the right, on the same ration, developed xerophthalmia in both herself and young, which was cured in both by the administration of butter fat to the doe.

The mature rabbit on the left in the accompanying figure is a representative animal from the group on the above ration. This animal is much more vigorous than the one on the right and the difference in vigor is much greater than is apparent in the picture, which was taken at the time the butter fat feeding was begun. Up until the birth of the young, the two grown rabbits were equally vigorous. The mother rabbit on the right shows xerophthalmia which is indicated by the fact that the eyelids are swollen nearly shut. A typical film had developed on this eye at the time this photograph was taken. It is evident that the strain of reproduction and lactation brought about this symptom of the deficient diet which would otherwise not have become apparent. We are now studying the effect of breeding on the production of symptoms of dietary deficiency using the males of this group of animals on their present diet.

A PECULIAR ERUPTIVE DISEASE OCCURRING IN INFANCY *

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AND

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Zahorsky ¹ in 1910, and again in 1913, described a symptom complex under the designation of "roseola infantum," which he believed deserved a nosologic position of its own.

His description of the condition is as follows:

"The patient is almost always a child under 3 years of age who suddenly becomes ill with high fever. The physician is called, and on examination finds nothing to account for the fever. The fever continues but no diagnosis can be made on the second, third or even fourth day. Then the temperature drops to normal, or nearly so, and the child, who has been drowsy and irritable, sits up and commences to play. Coincidentally with the decline in the temperature a morbilliform rash appears on the face and neck and rapidly spreads over the body. The eruption disappears in from twenty-four to forty-eight hours. There are no complications or sequels. No desquamation follows the disappearance of the rash."

This syndrome had been recognized previously ² but apparently had been classified with the toxic erythemas or, perhaps, as an atypical rubella.

Recently Levy,³ Veeder and Hempelmann,⁴ Greenthal ⁵ and Westcott,⁶ published their observations of, and incited interest in the condition. The clinical descriptions of these authors agree almost completely, though in some minor details their observations vary.

Since February, 1920, one of us (J. H. P.) has observed twenty-one cases of this disorder. To illustrate the condition more fully a typical case will be described.

* Received for publication, March 24, 1922.

1. Zahorsky, J.: *Roseola Infantum*, J. A. M. A. **61**:1446 (Oct. 18), 1913; *Pediatrics*, **22**:60 (Jan.), 1910.

2. Meig and Pepper's *Diseases of Children*: quoted by Zahorsky.

3. Levy, D. J.: *An Eruptive Fever of Unusual Characteristics in Infancy and Childhood*, J. A. M. A. **77**:1785 (Dec. 3), 1921.

4. Veeder, B. S. and Hempelmann, T. C.: *A Febrile Exanthem Occurring in Childhood (Exanthem Subitum)* J. A. M. A. **77**:1787 (Dec. 3), 1921.

5. Greenthal, R. M.: *An Unusual Exanthem Occurring in Infants*, Am. J. Dis. Child. **23**:63 (Jan.), 1922.

6. Westcott, T. S.: *Pseudo-Rubella*, Am. J. Med. Sc. **162**:267 (Sept.) 1921.

REPORT OF CASE

History.—Baby R. M., age 8 months, artificially fed, was perfectly well until Oct. 22, 1921. Without prodromata of any sort she became acutely ill. When the child refused a feeding the mother took her temperature and found it to be 103 F., by rectum. Two hours later the temperature was 104 F. The child was irritable, but was not toxic.

Physical Examination.—The physical examination was negative, save for moderate redness of the pharynx and a distinct redness of the posterior quadrants of each ear drum. Urinalysis was negative. A blood count showed: leukocytes 6,600; lymphocytes 82 per cent. Paracentesis of both drums was performed but no discharge followed and there was no drop in temperature.

Clinical Course.—The following morning the temperature was 102.4 F. but mounted toward evening to 104.2 F. The next morning it was 100.4 F. and remained above 101 F. all day. A leukocyte count this day was 5,600 with 87 per cent lymphocytes. On the morning of the fourth day, the temperature was 100.8 F.; by that evening it had fallen to 99 F. (During these days there was no apparent cause for the fever).

At this time a rash appeared, at first on the buttocks, back and chest, and rapidly spread to the back of the neck and scalp and the rest of the trunk. The extremities remained comparatively free. The eruption consisted of closely aggregated pale pink macules or slightly elevated maculopapules. The rash was profuse and confluence led to the formation of several irregular macules of comparatively large dimensions. A few of the lesions possessed urticarial features.

The temperature remained normal from the time of the appearance of the eruption, and thereafter the patient appeared as well as before the illness began.

The eruption reached its height in twenty-four hours, and involuting rapidly, disappeared in another twenty-four hours. No desquamation ensued.

ANALYSIS OF CASES

A picture of the symptomatology from the cases observed is as follows:

Onset.—This was abrupt in all cases, the child being apparently well the day before the illness began. Usually the mother or attendant discovered that the child was warmer than usual, and on taking the temperature, found it to be from 101 to 105 F. by rectum. Fretfulness and irritability were almost invariably present. Prostration was lacking, as well as gastro-intestinal symptoms.

Fever.—The fever mounted rapidly, reaching as high as 105 F. on the first day, but usually reached its maximum on the second or third day. It continued high, with moderate matutinal remissions for from three to five days, when it dropped suddenly to normal or subnormal. Practically all cases pursued the same febrile course. In an occasional case, the fever fell by lysis.

Pulse and respiration were in normal ratio to the temperature.

Eruption.—With the fall in temperature a rash appeared. It was first noted most often either on the buttocks or on the sides of the neck, beginning as discrete macules from 2 to 3 mm. in diameter. It appeared rapidly on other parts, and at its height was usually most

profuse on the trunk, and least intense on the extremities. Typically, it presents a distinctly morbilliform aspect. The lesions are pink to rose colored, fairly well defined, either absolutely level with the sound skin, or occasionally slightly raised maculopapules. They may be entirely discrete, but in some cases presenting a profuse rash confluence occurred, with the formation of lesions several centimeters in dimensions. No enanthem was ever noted. The efflorescence reached its height in twenty-four hours, lasted another day, and disappeared without desquamation.

Physical Findings.—Repeated examinations failed to furnish adequate cause for the fever. In one case there was a distinct redness of the posterior half of each ear drum, and in several other cases there was



Fig. 1. Baby B., aged 4 months. White blood cell count, 5,200; lymphocytes, 86 per cent. Typical rash appeared on fourth day and disappeared entirely on sixth day. No desquamation.

moderate congestion of the pharynx, tonsils, and soft palate. The lungs and heart were normal, as were the other viscera. There was no adenopathy.

Laboratory Examinations.—Twenty-two blood counts were made in eighteen cases. The highest leukocyte count was 7,800 and the lowest 4,800. Four counts were between 4,500 and 5,500; thirteen between 5,600 and 6,500, and five between 6,500 and 8,000.

In two cases the lymphocytes were between 65 and 75 per cent.; in seventeen cases between 76 and 85 per cent., and in three cases more than 85 per cent.

Leukopenia with lymphocytosis occurred in all of our cases in which the blood was studied. These findings occur at all times during the pre-

eruptive stage, and in conjunction with the clinical symptoms present a picture which is definite and characteristic. Veeder and Hempelmann and Greenthal likewise noted the leukopenia and lymphocytosis, which seems to be an essential part of the syndrome.

In one case a blood culture was negative. All urinalyses were negative, save for minor transitory changes, such as occur in any febrile condition.

Complications.—There were none.

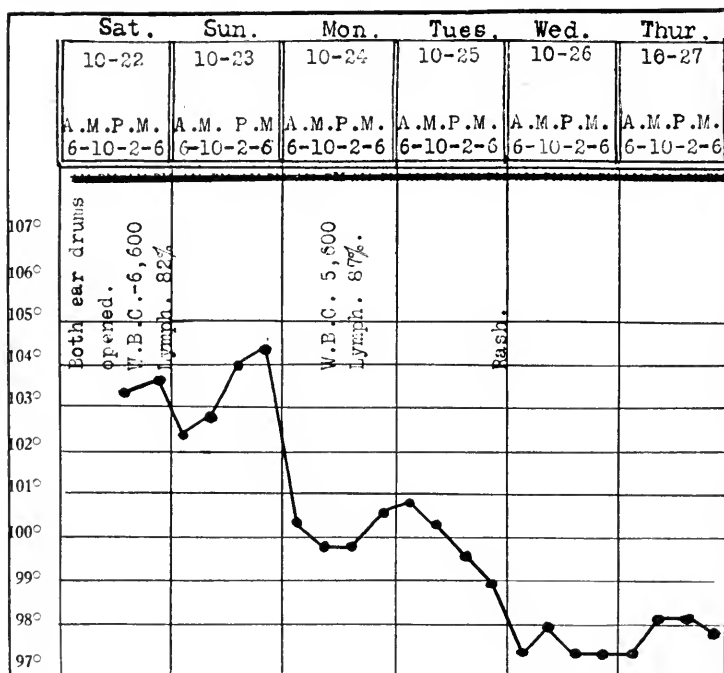


Chart 1.—Temperature chart of Baby R. M., illustrating fall of temperature by lysis.

Age Incidence.—The youngest patient was 4 months of age; the oldest 2 years.

Sex.—Ten patients were males, eleven were females.

Feeding.—Fourteen patients were completely artificially fed; seven received both breast and bottle. None was entirely breast fed.

Communicability.—In no instance was there evidence of contagion, nor have two cases occurred in the same family. There has been no recurrence.

Diagnosis.—In the preeruptive stage, otitis media, influenza, concealed pneumonia, typhoid and pyelitis are suspected, but can be ruled

out by appropriate examination as well as by the further course of the disease.

Of the exanthems only rubella and measles need be considered seriously. The later can be excluded by the absence of catarrhal symptoms and Koplik spots; by the continuance of fever after the appearance of the eruption, and by desquamation. Rubella has a short prodromal period and the fever rises with the eruption. There is postcervical adenopathy and desquamation. In each of these diseases contagiousness is a feature.

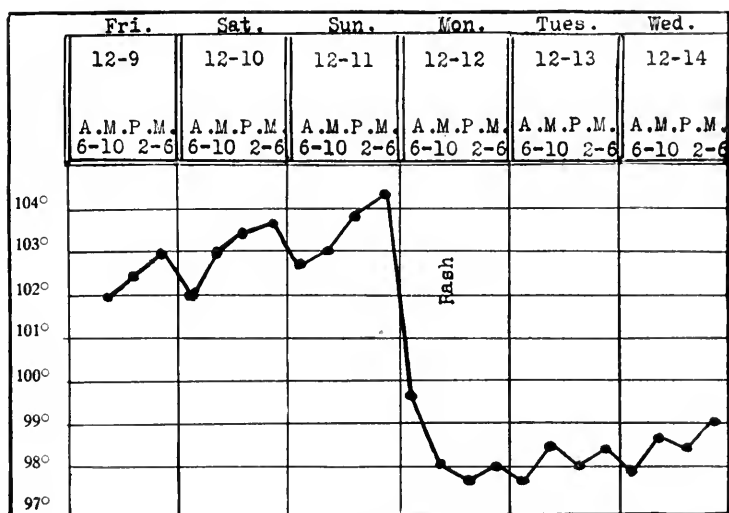


Chart 2.—Temperature chart of Baby B—showing fall of temperature by crisis.

Toxic erythemas may be considered. The rash in this condition may closely simulate the one under consideration, but in toxic erythema, a definite preeruptive stage is lacking. Drug rashes have been eliminated by the history. The fact that the eruption is noncontagious has led us to consider, seriously an allergic etiology. We contemplate doing protein sensitization tests as the opportunity arises.

DISCUSSION

Our own experience and that of others leads us to believe that this disorder is a definite clinical entity. The outstanding features are the abrupt onset, the high fever of from three to five days duration without apparent cause, and the appearance of a morbilliform rash coincident with a critical fall of temperature to normal. Additional points of distinction are the apparent non-contagiousness, and the predilection of the disease for infancy. Moderate leukopenia and lymphocytosis appear to be the only significant laboratory findings.

In reviewing the reports of others, we have noted the practically complete accord of all observers as to the clinical course of the disease. There are, however, some discrepancies in the observations which should be noted. For instance, Zahorsky, Westcott, and Levy found enlargement of the superficial cervical lymph nodes, especially the posterior group, in a large majority of their cases. Veeder and Hempelmann, Greenthal and ourselves have not observed any significant adenopathy.

Veeder and Hempelmann, and Greenthal noted very slight desquamation in a few of their cases, while other observers are unanimous in stating that it is absent. In our experience desquamation has never followed the involution of the eruption.

CONCLUSIONS

The pertinent facts of twenty-one cases of an unusual disorder occurring in infancy and childhood have been recorded.

This condition is distinctive and appears to be a clinical entity. We are able to confirm the findings of others that leukopenia and lymphocytosis occur with such uniformity as to be of significance. We have, likewise, noted an entire lack of contagiousness. The etiology is unknown.

THE VALUE OF THE INTRACUTANEOUS TUBERCULIN TEST IN EXTENSIVE TUBERCULOSIS *

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BALTIMORE

The belief is quite general that the skin hypersensitiveness to tuberculin is frequently lost in the presence of an overwhelming tuberculous infection, such as general miliary tuberculosis and tuberculous meningitis. This belief is based on repeated statements to that effect in textbooks and articles dealing with the tuberculin skin test. Since we accept the fact that skin hypersensitiveness to tuberculin means that there is a focus of tuberculous infection somewhere in the body, if the reaction is frequently lost in one of the forms of tuberculosis in children in which diagnosis is most difficult, i. e., miliary tuberculosis, then the test loses much of its importance.

The statistics on the tuberculin test, especially in children, are based mainly on the results obtained with the Pirquet skin test. Hess¹ tested twelve cases of tuberculous meningitis and found 17 per cent. positive. Dunn and Cohen² tested 120 cases of miliary tuberculosis and tuberculous meningitis, with 59.8 per cent. positive. Meyers³ tested 105 cases of tuberculous meningitis with 63 per cent. positive. From these figures it appears that in generalized tuberculosis negative reactions with the most commonly used test are obtained in 40 per cent. of the cases. On the basis of the Pirquet test there is thus some ground for the belief expressed above.

It is apparent from the literature that with the method extensively utilized by Hamburger⁴ (Stichreaktion of Escherich—a subcutaneous injection method) a greater number of positive results are obtained in the presence of severe tuberculosis than by the cutaneous method.

We determined to use the intracutaneous method of Mantoux⁵ which was devised as long ago as 1908, but has been comparatively little used with children, except by Jeanneret,⁶ chiefly as a therapeutic method. As usually employed, it has given positive results hardly better

* Received for publication, March 3, 1922.

* From the Department of Pediatrics, the Johns Hopkins University and the Harriet Lane Home, the Johns Hopkins Hospital.

1. Hess, J. H.: *M. Clinics N. America* **1**:1357, 1918.

2. Dunn, C. H., and Cohen, S. A.: *Am. J. Dis. Child.* **21**:187, 1921.

3. Meyers, A. E.: *Am. J. Dis. Child.* **9**:427, 1915.

4. Hamburger, F.: *Die Tuberkulose des Kindesalters*, Leipzig and Wien., Franz Deuticke, 1912.

5. Mantoux, C.: *Compt. rend. Acad. d. Sc., Par.* **147**:355, 1908.

6. Jeanneret, L.: *La Tuberculose de l'Enfant*, Paris, 1915.

in frequency or regularity than the Pirquet cutaneous test. Bass'⁷ experience is an exception to this. He found the intracutaneous test definitely more satisfactory than the Pirquet cutaneous test in detecting mild degrees of tuberculous infection in apparently well children. Certainly, the intracutaneous test is sensitive, and with care and experience yields accurate results. We employed it on the suggestion of Dr. A. K. Krause that the ability of the tuberculous to react to tuberculin in overwhelming tuberculous infection is not lost but merely depressed, because the Mantoux method allows the use of accurately measured amounts of tuberculin. It is thus possible to begin with a small amount and increase the amount at subsequent injections, provided there is no positive reaction with the smaller quantity.

For the tests we used old tuberculin obtained from Dr. E. R. Baldwin at the Saranac Laboratory and from Dr. A. K. Krause's laboratory at Johns Hopkins Hospital. Dilutions were made in 0.85 per cent. sterile saline solutions with 0.25 per cent. phenol as a preservative, and graded so that 0.1 c.c. of the solution contained the amount to be injected. The solutions were kept in dark bottles in the refrigerator and were made fresh once a month. They remained sterile. The amounts used were 0.01 mg., 0.1 mg., 1 mg., and in a few instances more than 1 mg. As a control solution we used equivalent amounts of glycerin broth diluted as above with phenol preservative and of the same concentration as the glycerin broth of the old tuberculin. This is the only solution that can be considered a true control. The tests were made and were read at the end of twenty-four and forty-eight hours. A definite erythema or erythema and induration 0.5 cm. or more in diameter was considered positive, provided the control was entirely negative.

The amount of tuberculin advisable to use for the first test depends on the condition of the patient. Krause⁸ and Willis⁹ found that a general reaction of an anaphylactic character can be produced in nontuberculous guinea-pigs after repeated injections of tuberculin but never was a local (tissue) reaction obtained. This anaphylactic reaction bore no relation to the general tuberculin reaction and must not be confused with it. Similarly Hamburger⁴ was never able to obtain a local reaction from tuberculin in the nontuberculous human being. He gave as much as 1,000 mg. with negative results. On the other hand, great care must be observed when tuberculosis is suspected, for not only may the arm become swollen and painful but occasionally sloughing occurs at the point of injection when too large an amount is given. Also, the excitation of a general reaction with fever and an activation of the

7. Bass, M. H.: *Am. J. Dis. Child.* **15**:313, 1918.

8. Krause, A. K.: *J. M. Research* **19**:361, 1911.

9. Krause, A. K., and Willis, H. S.: *Am. Rev. Tuberc.* **3**:153, 1919.

tuberculous condition at the focus or foci of infection may occur. For these reasons the amount for the initial injection should be small, and then, if no reaction takes place, the next higher concentration may be given, and so on. For routine tests with children we used 0.01 mg. as an initial injection. Some patients will react to 0.001 mg., but a violent reaction following the injection of 0.01 mg. is most uncommon. In order to obviate unnecessary tests, 0.01 mg. was usually given as a routine measure for the initial injection when the forms of tuberculosis which present in the patient the greater skin sensitiveness were suspected, namely, tuberculous conjunctivitis or keratitis, skin manifestations, superficial glandular, osseous, early active pulmonary, pleuritic or renal. The next higher concentration (0.1 mg.) was employed as the initial injection only when a depression of skin sensitiveness might be assumed, for instance, with generalized tuberculosis and tuberculous meningitis.

In order to compare the results of our intracutaneous tests with those of the Pirquet cutaneous test, we did Pirquet tests in most instances at the same time as the intracutaneous tests. For statistical purposes we have included the results of Pirquet tests upon previous cases of miliary tuberculosis and tuberculous meningitis when the diagnosis had been confirmed by necropsy or by finding tubercle bacilli. The results of both tests are presented in Tables 1 and 2.

TABLE 1.—CASES OF MILIARY TUBERCULOSIS INCLUDING TUBERCULOUS MENINGITIS IN WHICH TUBERCULIN SKIN TESTS WERE PERFORMED

	Pirquet			Per Cent.	Intracutaneous			Per Cent.
	No.	+	0		No.	+	0	
Miliary tuberculosis with meningitis.....	113	79	64	55.2	53	49	4	92.4
Miliary tuberculosis without meningitis.....	40	15	25	37.5	19	14	5	73.6
Total.....	153	94	89	51.3	72	63	9	87.5

TABLE 2.—NUMBER OF POSITIVE REACTIONS OBTAINED IN MILIARY TUBERCULOSIS INCLUDING TUBERCULOUS MENINGITIS WITH GRADED AMOUNTS OF TUBERCULIN ADMINISTERED INTRACUTANEOUSLY

Amount in Mg.	0.01	0.1	1.0	More Than 1.0
Number positive.....	12	48	15	5
Number negative.....	12	12	1	0
Percentage positive.....	50	80	93.7	100

It should be emphasized that these tests were performed on patients with advanced generalized tuberculosis and contrary to the belief of Jeanneret⁶ and others that under such circumstances the sensitiveness to tuberculin usually disappears five days, a week, or more before death;

most of our intracutaneous tests happened to be performed and reactions obtained during the four days prior to death. As many as 41 per cent. were obtained during the last two days before death and 22 per cent. on the last day of life.

Of those to whom 0.01 mg. was given, 50 per cent. reacted (Table 2) which is about the same percentage that reacts to the Pirquet skin test. By doing parallel Pirquet and intracutaneous tests on all patients admitted to the hospital, we received further convincing evidence that the sensitiveness to tuberculin is quantitative and that the frequency of reaction after the employment of the Pirquet cutaneous test is nearly the same as that with 0.01 mg. of tuberculin given intracutaneously.

Finally, it is but fair to the intracutaneous test to say that the nine negative tests (Table 1) were obtained in patients who either did not live long enough or did not remain in the hospital long enough to receive more than the smaller amount of tuberculin. We feel that had it been possible to give them the higher concentrations, all or nearly all would have reacted, for as seen in Table 2 all except one who received as much as 1 mg. reacted, and the few to whom we gave more than 1 mg. gave marked reactions. Only occasionally, in a patient with far advanced generalized tuberculosis and extreme emaciation, was more than 1 mg. tuberculin ever required to excite a reaction.

CONCLUSIONS

1. In miliary tuberculosis and tuberculous meningitis in infants and children the Pirquet cutaneous test was positive in just over 50 per cent. of our cases.

2. A failure to react to the Pirquet test in miliary tuberculosis and tuberculous meningitis does not mean a loss but only a depression of skin sensitiveness to tuberculin.

3. The tuberculin test is quantitative and the Pirquet cutaneous test is equivalent to about 0.01 mg. tuberculin given intracutaneously.

4. The intracutaneous test is more sensitive and as opposed to the Pirquet test it not only affords a method of accurately measuring the amount of tuberculin given, but enables one to increase the amount at will.

5. If a high enough concentration of tuberculin is given intracutaneously, a positive reaction will be obtained in practically all cases of tuberculosis.

THE BACTERIOLYSANT THERAPY OF BACILLARY DYSENTERY IN CHILDREN *

THERAPEUTIC APPLICATION OF BACTERIOLYSANTS; D'HERELLE'S
PHENOMENON

WILBURT C. DAVISON, M.D.

BALTIMORE

It has been demonstrated by d'Herelle and others¹ that if a small portion of feces from a dysenteric convalescent or even from a normal person is inoculated in a flask of bouillon, and this mixed culture is passed through a Berkfeld filter, the resulting sterile filtrate, when added to young cultures of dysentery and other bacilli, will kill and dissolve the organisms. If a portion of this dissolved culture is, in turn, added to another young dysentery culture, the organisms will again be killed and dissolved. This phenomenon can in this way be reproduced for innumerable successive generations. The names bacteriophage, bacteriolysant and lytic agent have been given to these filtrates. When they are injected intravenously and subcutaneously into rabbits and other animals, no harmful effects are produced. These animals develop antibodies for the organisms against which the filtrates are active. It was obvious to many observers that these filtrates which would kill and dissolve dysentery bacilli in vitro, which were non-pathogenic and would immunize animals, should be tried therapeutically in clinical cases of dysentery. However, the question arises as to whether the administration of an antidysentery bacteriophage to dysentery patients might not possibly be harmful. The intestinal lesions of dysentery are probably caused by an endotoxin, and it would seem logical to assume that if dysentery bacilli in the intestinal tract were killed and dissolved as the result of the administration of a bacteriophage, a large amount of endotoxin would be liberated. Nevertheless Kabeshima and others¹ have demonstrated that injections of an antidysentery bacteriophage into rabbits infected with dysentery bacilli are harmless. I have injected large amounts of these filtrates into a rabbit and am convinced that they are innocuous. Inasmuch as Flexner dysentery in children is one of our worst diseases, and as

* Received for publication Feb. 23, 1922.

¹ From the Department of Pediatrics, the Johns Hopkins University and the Harriet Lane Home, the Johns Hopkins Hospital.

1. A summary of the literature and a complete bibliography is given in Davison, W. C., Bibliographic review of bacteriolysants (d'Herelle's phenomenon), Abstr. Bacteriol., Baltimore, 1922 (in press).

serotherapy² and our present treatment are ineffectual in reducing the high mortality, I felt justified in cautiously proceeding with bacteriolysant therapy during the summer of 1921.

Bacteriolytic filtrates active against one or more strains of Flexner bacilli were obtained by d'Herelle's method. The bacteriolytic activity of these filtrates was tested in eight instances against the organism isolated from the patients' stools and in seven the filtrates were found to be active. The method of obtaining these filtrates and testing their activity is described elsewhere.³

These filtrates were administered to twelve infants, aged from 2 months to 4 years, suffering from bacillary dysentery (Flexner). Clinically these children represented typical cases of this disease.⁴ *B. dysenteriac* (Flexner), and by that I refer to the whole group of mannite fermenting dysentery bacilli,⁵ were isolated from the stools of ten of the twelve patients. The individual dose of the bacteriolysant was from 5 to 198 c.c. and was given from one to ten times. The interval between doses was from four to twenty-four hours. The total amounts administered to any one child varied from 5 to 1,381 c.c. Seven children drank the filtrates from a cup or a nursing bottle (the taste is very similar to that of broth); in five cases the filtrates were introduced by rectum with a high enema tube; to two patients they were given by gastric gavage together with the feedings of protein milk. In two infants, in addition to rectal administration, the filtrates were introduced into the stomach through a constant drip nasal tube together with the saline that was being used to maintain the body fluid.

Nine of these twelve patients had severe infections and seven of them died, a mortality of 78 per cent. Three had moderate infections and none died, making a total mortality for the twelve cases of 58 per cent. These figures are practically identical with those we have previously published² for severe and moderate dysenteric infections in children, both untreated cases and those treated with subcutaneous and intramuscular injections of antidysenteric serum. In no instance did the patient seem any the worse for the treatment. One patient's stools decreased in number after rectal treatments with a filtrate but inasmuch as the bacteriolytic filtrate used, though active against another strain of the Flexner bacillus, had but slight lytic action on the organisms isolated from this patient's stools, it may be concluded that the improve-

2. Josephs, H. W., and Davison, W. C.: The Serotherapy of Bacillary Dysentery in Children, *J. A. M. A.* **77**:1863 (Dec. 10) 1921.

3. Davison, W. C.: Observations on the Nature of Bacteriophages, Bacteriolysants, Lytic Agents, d'Herelle's Phenomenon, *Proc. Soc. Am. Bacteriologists*, Dec. 29, 1921; *J. Bacteriol.*, 1922 (in press).

4. Davison, W. C.: Bacillary Dysentery in Children, *Bull. Johns Hopkins Hosp.* **21**:225, 1920.

5. Davison, W. C.: Divisions of the So-called Flexner Group of Dysentery Bacilli, *J. Exper. M.* **32**:651, 1920.

RESULTS OF ADMINISTRATION OF DYSENTERY BACILLUS BACTERIOLYSANT

Case No.	Age	Race	Stool Culture	Degree of Severity of Infection	Method of Administration of Bacteriolysant	Days After Onset of Which First Dose of Bacteriolysant Was Given	Number of Doses of Bacteriolysant Given	Interval Between Doses, Hours	Amount of Each Dose, C.c.	Total Amount of Bacteriolysant Given, C.c.	Lytic Activity of Bacteriolysant Against Dysentery Bacillus Isolated from Patient's Stool	Duration of Disease, Days	Final Outcome of Patient	Effect of Bacteriolysant
29271	2 mos.	White	B. dysenteriae (Flexner) Negative	Severe	Rectal injection (bottle)	11	2	8	34-35	80	Slight	17	Recovered	No effect
29556	15 mos.	White		Severe	By mouth (bottle)	16	2	24	38-60	96	Not tested	20	Died	No effect
29627	12 mos.	White	B. dysenteriae (Flexner)	Severe	By mouth (gavage)	13	3	8-12	80-100	280	Strong	15	Died	No effect
29717	12 mos.	Colored	B. dysenteriae (Flexner)	Severe	By mouth (bottle and gavage)	20	3	4-16	45	135	Not tested	21	Died	No effect
29010	6 mos.	Colored	B. dysenteriae (Flexner)	Severe	Rectal injection and nasal drip	13	4	6-12	55-126	323	Strong	14	Died	No effect
29565	14 mos.	White	B. dysenteriae (Flexner) Negative	Severe	By mouth (bottle)	26	4	7-12	30-60	195	Strong	39	Died	No effect
29272	2 mos.	White		Severe	Rectal injection	11	6	8-17	25-40	170	Not tested	13	Died	No effect
29413	7 mos.	White	B. dysenteriae (Flexner)	Severe	Rectal injection	6	6	5-24	25-50	250	Slight	24	Recovered	Apparent benefit
29569	3 mos.	White	B. dysenteriae (Flexner)	Severe	Rectal injection and nasal drip and by mouth (bottle)	8	10	6-24	55-198	1,381	Strong	18	Died	No effect
29456	9 mos.	White	B. dysenteriae (Flexner)	Moderate	By mouth (bottle)	16	1	40	40	Not tested	21	Recovered	No effect
29622	2½ yrs.	White	B. dysenteriae (Flexner)	Moderate	By mouth (cup)	16	1	72	72	Strong	?	Recovered	No effect
29700	4 yrs.	White	B. dysenteriae (Flexner)	Moderate	By mouth (cup)	1	1	5	5	Negative	9	Recovered	No effect

ment was due to the cleaning of the lower colon by the rectal irrigation rather than to the bacteriolytic action of the filtrate. In none of the other children was there any apparent effect on the course or duration of the disease. No systematic study was made to determine the effect of the treatment on the rate of disappearance of the dysentery bacilli from the stool. In Case 29,569, *B. dysenteriae* (Flexner) were isolated from the stools twenty-four hours after the last of ten doses of bacteriolysant. The total amount of filtrate given this patient was 1,381 c.c. It is interesting to note that the bacteriolysants used in this case lysed the dysentery bacilli isolated after the treatment in higher dilutions than the organism isolated shortly after the onset of the disease, so that is fair to assume that this patient did not die because his organisms became resistant to the filtrates.

The failure of bacteriolysant therapy in this series may possibly be explained on the ground that the treatment in the majority of the cases was commenced late in the disease. The only two patients treated within the first week after the onset of the disease recovered. However, this criticism is met by the large amounts of filtrate used, coupled with the fact that two-thirds of the deaths from bacillary dysentery in children, whether treated or not, occur within the first twelve days² and that patients surviving that period have a much better chance of recovery.

D'Herelle,¹ on the other hand, has reported striking cures from bacteriophagic therapy in seven adults suffering from dysentery as well as in animals afflicted with various infections. Larger series alone will demonstrate the practical value of bacteriolysants.

CONCLUSION

As far as can be judged from this limited series of cases of bacillary dysentery in children, in which bacteriolytic filtrates in amounts of from 5 to 1,381 c.c. were administered, bacteriolysant therapy did not influence the mortality or the course of the disease.

PROGRESS IN PEDIATRICS

A REVIEW OF THE LITERATURE OF SYPHILIS IN INFANCY AND CHILDHOOD *

PARK J. WHITE, M.D.

ST. LOUIS

(Concluded from page 469)

GENERAL OBSERVATIONS ON HEREDITARY SYPHILIS

Stoll¹⁴⁸ gives a review of the various clinical signs of the disease—naturally a subject to which but little has been added. He makes some timely remarks on the ease with which the smaller signs may be missed, and the Wassermann test be omitted as a result. Stoll describes a sign which might well be due to other conditions, but which he has frequently encountered in hereditary syphilis—namely, an increase in the normal carrying angle of the elbow, which he has called the “knock-knee elbow,” and which is due to overgrowth of the internal condyle of the humerus. It occurs sometimes with limitation of extension. Other general discussions of the symptomatology of hereditary syphilis are those of Beeson¹⁴⁹ and of Langstein.¹⁵⁰

MISCELLANEOUS OBSERVATIONS

Thiroux¹⁵¹ notes that the influence of syphilis on the development of athrepsia is not a new question; but that the existence of athrepsia exclusively syphilitic has not been sufficiently emphasized. His studies were made in Indo-China, where syphilis is extremely common. The manifold causes of athrepsia in such a population are given full weight. He reports one breast fed baby (with an apparently healthy mother) practically moribund from vomiting and diarrhea. Dramatically rapid improvement followed intensive antisyphilitic treatment without other change. He adds the report of a similar case, calling attention to the possibility, especially in Indo-China, of purely syphilitic enteritides.

Almkvist¹⁵² found that the weight gradually declines under mercurial treatment and increases under arsphenamin. He strongly urges especial attention to diet in cases receiving mercury.

Blechnann¹⁵³ presents evidence to show that inherited syphilis is often responsible for different forms of jaundice in infants, hitherto

* From the Department of Pediatrics, Washington University.

148. Stoll: J. A. M. A. **77**:919 (Sept. 17) 1921.

149. Beeson: Illinois M. J. **40**:222 (Sept.) 1921.

150. Langstein: Deutsch. med. Wchnschr. **47**:449 (April 21) 1921.

151. Thiroux: Bull. de l'Acad. de méd., Par. **84**:215 (Nov. 9) 1920.

152. Almkvist: Hygiea, Stockholm, **83**:363 (June 16) 1921; abstr. J. A. M. A. **77**:416 (July 30) 1921.

153. Blechnann: Nourrisson **8**:145 (May) 1920.

ascribed to other causes, or even regarded as physiologic. The occurrence of jaundice, in his opinion, calls for scrupulous investigation for syphilis.

Gelston¹⁵⁴ says that syphilis without doubt plays a part, and an important one, in certain cases of hemorrhagic disease of the new-born.

Castex and del Valle¹⁵⁵ regarded hereditary syphilis as a frequent, perhaps the most frequent, cause of membranous perenteritis and analogous conditions. The intestinal stasis in these cases is attributed to endocrine disturbances secondary to syphilis; and the resulting chronic inflammation of the colon spreads to the surrounding serous membrane. Surgery in such cases should, of course, be limited to those which resist antisyphilitic treatment, or in which adjacent organs become inflamed.

An unusual case report is that of a girl, aged 9, studied by Maggesi.¹⁵⁶ She developed attacks of high fever lasting for two or three days, with intervals of a few days. There was no chill, no profuse sweating, and the general condition continued fair. An eruption finally accompanied the attacks and retrogressed with them. The positive Wassermann and negative malaria search were confirmed by cure under mercurial treatment.

Three case reports by Lornholt¹⁵⁷ are of interest as showing the necessity for vigilance for the possibility of infants acquiring syphilis from the mother, at birth. He cites from the literature two cases of infants infected by the mother at birth. In these and in his own three cases, the mother was infected late in pregnancy, and at confinement had open sores on the pudenda. In four infants chancres were found on the scalp; in the fifth case, on the cheek. The chancres were multiple in all cases. The maternal secondaries were undetected until confinement or shortly afterward. Handowsky¹⁵⁸ reports a typical chancre on the lip of an infant 11 months old, with rapid improvement on antiluetic treatment.

Ugon¹⁵⁹ gives interesting data on three women who developed multiple mammary chancres while nursing children who were not suspected of syphilis. One of the women infected another child she was nursing at the time.

PATHOLOGIC STUDIES

Warwick's necropsy findings in 200 new-born infants have already been mentioned.¹² Browne's findings in a series of 200 still-births

154. Gelston: *Am. J. Dis. Child.* **22**:351 (Oct.) 1921.

155. Castex and del Valle: *Surg., Gynec. & Obst.* **31**:160 (Aug.) 1920.

156. Maggesi: *Riv. critica di clin. med.* **22**:253 (Aug. 5) 1921; abstr. *J. A. M. A.* **77**:1211 (Oct. 8) 1921.

157. Lornholt: *Ann. de dermat. et syph. Series 6*—2:17 (Jan.) 1921.

158. Handowsky: *Ztschr. f. Kinderh.* **28**:216 (March 21) 1921.

159. Ugon: *Arch. Latino-Amer. de Pediat.* **14**:241 (May and June) 1920; abstr. *J. A. M. A.* **75**:1099 (Oct. 16) 1920.

have also been discussed.¹¹ In his discussion of pathology, he emphasizes the lesions in the thyroid (especially fibrosis), the thymus (also fibrosis), the lung, and the liver (periportal cirrhosis). In his later article,¹⁶⁰ he reports splenic enlargement (virtually diagnostic when present) in only five cases, the largest weighing 55 gm. In all cases the enlargement was associated with periportal cirrhosis of the liver. The *spirochaeta pallida* was found in eight cases of fourteen known syphilitic macerated fetuses. In twenty-one fresh fetuses, it was found in only one. One of the fresh fetuses in which it was not found was the twin of a macerated fetus in which numerous spirochetes were present. Browne believes that the placenta is virtually of no value in the diagnosis of syphilis in the full time infant; but that it may give strong additional evidence in premature and macerated fetuses.

The phenomenon of "immediate death" in heredosyphilitic infants is discussed editorially,¹⁶¹ the term immediate death meaning death occurring two or three minutes after birth. The lungs are frequently the seat of inflammatory changes, and the liver and spleen are rarely intact. Ascites is generally present. There are some cases in which the most careful necropsy has failed to reveal any determining cause for sudden death. Bonnet is quoted as believing that the real cause is often the impossibility of pulmonary expansion, on account of the hypertrophy of the abdominal viscera.

An important, exhaustive study of the visceral changes in hereditary syphilis has recently been published by Fraser.¹⁶² The results of his investigations are too numerous and detailed to be abstracted here. His article should be read by every student of the subject.

It is Fletcher's opinion¹⁶³ that in hereditary syphilis resistance to other infections is greatly lowered, and he considers this especially true of tuberculosis. He describes the morbid changes in heredosyphilitic kidneys. In the fetus, groups of embryonal cells surrounded by normally developed tissue, and small cell infiltration of the cortex, constitute the common lesions. In infants and older children sclerosis is much more marked.

Rolleston⁵⁵ also notes that hereditary syphilis should be considered a factor predisposing to other infections. He believes that multilobular or portal cirrhosis may very frequently be heredosyphilitic in origin.

Lemaire et al¹⁶⁴ present the necropsy findings in a case (age 2 months) of intestinal hemorrhage of syphilitic origin. The examination was negative except in the intestine. In the ileum and jejunum there

160. Browne, F. J.: *Edinburgh M. J.* **27**:199 (Oct.) 1921.

161. *Med. Rec.* **100**:946 (Nov. 26) 1921.

162. Fraser: *J. A. M. A.* **77**:1623 (Nov. 19) 1921.

163. Fletcher: *Lancet* **1**:630 (March 26) 1921.

164. Lemaire, Blechmann, and Turquety: *Nourrisson* **9**:104 (March) 1921.

were multiple disseminated ulcers, also hemorrhagic areas, on the intestinal walls, with slight hyperplasia of the involved portion of the gut. There were no lesions of Peyer's patches.

Methods for the demonstration of spirochetes in the tissues are described by Haythorn,¹⁶⁵ by Warthin and Starry,¹⁶⁶ and by Jahnel.¹⁶⁷

TREATMENT

Prophylaxis.—It is clear from the recent literature that the prophylaxis of hereditary syphilis is obtaining the recognition it deserves. Fundamentally, of course, the prophylaxis of hereditary syphilis is the prophylaxis of the acquired disease. Improving economic conditions, providing better and more available public amusements, sex education—"general uplift," in short—must be given proper weight. But, in the language of Vernes,¹⁶⁸ "until such slowly operating methods can become effective" prophylaxis by medical means must be resorted to. Besides the local measures already in use, the arsphenamin prophylaxis described by Michel and Goodman¹⁶⁹ deserves mention. They have found that the administration of several doses of arsphenamin to patients known to have been exposed to syphilis—i. e., in the incubation period between exposure and initial lesion—is completely successful in preventing the appearance of the disease in many cases.

The subject of syphilis and marriage, discussed by Kleeberg,¹⁷⁰ is, of course, a most important one. His text is a woman of 39, apparently free from signs of syphilis since 1903 when she was given a course of inunctions. She had had fifteen pregnancies, and nearly all the children and fetuses showed inherited syphilis, most severe in the fifteenth child. He insists that every woman with a history of syphilis, regardless of the length of the interval since infection, should be given a course of energetic treatment when she becomes pregnant, unless there is absolute certainty that abortive treatment has eradicated the disease. Hata¹⁷¹ urges the necessity of educating the public, lay and professional, in the dangers of transmission of syphilis by women with positive Wassermann reactions without symptoms. He also recommends an educational campaign among midwives, thorough treatment of positive cases during pregnancy, insistence on examination of the blood of both partners, and the early treatment of syphilitic babies. Findlay¹⁷² believes that antenatal treatment can best be handled,

165. Haythorn: J. A. M. A. **76**:725 (March 12) 1921.

166. Warthin and Starry: J. A. M. A. **76**:234 (Jan. 22) 1921.

167. Jahnel: München. med. Wchnschr. **67**:1263 (Oct. 29) 1920.

168. Vernes: Internat. J. Pub. Health **2**:147 (March-April) 1921.

169. Michel and Goodman: J. A. M. A. **75**:1768 (Dec. 25) 1920.

170. Kleeberg: Med. Klin. **17**:962 (Aug. 7) 1921; abstr. J. A. M. A. **77**:1293 (Oct. 15) 1921.

171. Hata: Internat. J. Pub. Health **2**:354 (July-Aug.) 1921.

172. Findlay: Glasgow M. J. **96**:278 (Nov.) 1921.

and with the least degree of publicity for innocent women, by the family physician. He urges compulsory notification of all stillbirths, miscarriages and syphilitic children. Husten¹⁷³ and Browne¹¹ also urge notification, the latter, however, preferring that notification be voluntary.

Vernes¹⁶⁸ believes that methods like those used at the Institut Prophylactique (founded in Paris, 1916) are of great value, the fact that the records are confidential, the methods thorough, the laboratory facilities ample, making careful observation possible, and "prophylaxis by treatment" a reality. Couvelaire¹⁷⁴ describes a "maternity consultation dispensary," which "gathers the pregnant women and treats them and their fetuses." Attendance there has no stigma, and the women flock to it. Knowlton¹⁷⁵ remarks that the essential factors in preventing syphilis among children are the discovery and proper treatment of adult carriers of the disease—a corroboration of Heagerty's statement⁴⁹ that "wrapped up in the word latency is the key to the cure of syphilis" (and to its prevention in children).

Hendry¹⁷⁶ finds that when treatment is begun during pregnancy, the prognosis for the fetus depends on the unknown degree of infection already present in the fetus. In Routh's opinion,¹⁷⁷ if unrestricted infection has been going on in the early ovum or fetus, rapid destruction would result in spite of treatment. Jewesbury¹⁴ found that treatment begun after the seventh month of pregnancy did not prevent the birth of a syphilitic child—though subsequent cure of such a child could be effected more readily. The majority of those in whom treatment was begun not later than the fifth month had children free from syphilis. In Williams' ⁸ series, the comparative results obtained in treated and untreated mothers were most striking. He says that "There is every reason to hope that in future hereditary syphilis may be practically eradicated in clinics in which the mothers register prior to the middle of pregnancy." Adams,¹⁷⁸ Preuss¹⁷⁹ and Beck¹⁸⁰ submit further evidence of the value of prenatal treatment.

Sauphar¹⁸¹ urges that as two organisms—mother and child—must be protected, antisyphilitic drugs must be given in larger dosage during pregnancy. He adds that both doctor and patient must remember

173. Husten: *Arch. f. Kinderh.* **69**:319 (May 21) 1921; abstr. *J. A. M. A.* **77**:327 (July 23) 1921.

174. Couvelaire: *Gynéc. et Obst.* **4**:9 (July) 1921.

175. Knowlton: *Pub. Health Rep.* **36**:2305 (Sept. 23) 1921.

176. Hendry: *Lancet* **2**:986 (Nov. 13) 1920.

177. Routh: *Lancet* **2**:988 (Nov. 13) 1920.

178. Adams: *Lancet* **2**:990 (Nov. 13) 1920.

179. Preuss: *Therap. Halbmonatsh.* **35**:306 (May 15) 1921.

180. Beck: *Am. J. Obst. & Gynec.* **2**:416 (Oct.) 1921.

181. Sauphar: *La Médecine* **2**:569 (April) 1921.

that it is the syphilis and not the treatment that causes miscarriage; and in the event of abortion, it may be assumed that the treatment has been inadequate or begun too late.

Greenlees¹⁸² cites cases to show the inadequacy of antenatal treatment with mercury and potassium iodid alone, emphasizing the great advantage of combining these drugs with arsphenamin. He also notes that in spite of the absence of further treatment, the majority of the mothers continued to bear nonsyphilitic children. Success in producing a negative Wassermann in the mother seems not to be as complete as that in producing nonsyphilitic children. The author thinks it not incongruous that a woman with a positive Wassermann reaction should give birth to a healthy child. The spirocheticide has easy access to the organism in the highly vascular tissues of the uterus and placenta, though probably the positive Wassermann may be due to organisms inaccessible to the drug and for the same reason harmless to the child. He says it has not been definitely ascertained how late in pregnancy treatment may be begun and success expected.

Rawlins¹⁸³ goes so far as to urge antisymphilitic treatment for *all* women giving a history of miscarriages or stillbirths, even with a negative Wassermann. In her experience, colossal sulphur, or sublimed sulphur, or intramine, will help to prevent mercurialism and also to cure the syphilis. In discussing her paper, McKenzie urged that the medical profession teach venereal men and women methods of birth control. In the course of the same discussion, Walker said that rather than birth control, added facilities for treating syphilitic pregnant women were needed.

POSTNATAL TREATMENT; GENERAL OBSERVATIONS

All are agreed that treatment is of practically no avail as far as complete cure is concerned, unless it is given persistently and regularly over a long period of time. The essential part played by the social worker in achieving this end is coming to be more and more recognized. Solomon¹⁸⁴ says that a high percentage of success is secured only by the persistent follow-up and persuasion of the social worker. Without such a follow-up, many families ignore the appeal to report to the hospital. Smith¹⁸⁵ points out that these workers require special training, as they are frequently called on to handle most delicate situations with parents, employers, the courts, probation officers, etc. The financial difficulties in the way of one or other parent bringing children to clinics, are also emphasized by him.

182. Greenlees: *Glasgow M. J.* **96**:270 (Nov.) 1921.

183. Rawlins: *Brit. M. J.* **2**:194 (Aug. 7) 1920.

184. Solomon, M. H.: *Social Hygiene* **6**:93 (Jan.) 1920.

185. Smith, C. M.: *Arch. Dermat. & Syph.* **4**:723 (Dec.) 1921.

Mrs. B. Marshall¹⁸⁶ urges that parents of syphilitic children be seen by the social worker in the clinic in which the parents are treated, so that the efforts of both doctor and social worker can, if necessary, be combined to impress either or both parents with the necessity of having all the children examined. As might be expected, many mothers, when the situation is explained to them, are willing to cooperate. Others require, when everything else fails, resort to the Juvenile Court. One of the chief difficulties encountered by her was the common one met in trying to get parents to continue the children's treatment after the subsidence of acute manifestations.

Systematic plans of treatment have been outlined by several writers. Space does not allow the presentation of the details of each plan. Engel and Türk¹⁸⁷ do not use intravenous therapy during early infancy on account of the smallness of the veins. They prefer "novasurol" intramuscularly, and also mercury-protiodid. Intravenous arsenical medication is started after the first six months. Blechmann¹⁸⁸ urges intensive intravenous treatment with novasenobenzol, regardless of the age of the infant.

Fordyce and Rosen¹⁸⁹ give neo-arsphenamin and mercuric chlorid intramuscularly. A special needle for this purpose is described. The mercuric chlorid is put up in palmatin to favor its slow absorption (in three or four days). The authors claim that if neo-arsphenamin is given deeply enough into the muscle, abscesses and infiltrations can be avoided.

Jeans¹⁹⁰ describes the method used in his clinic in the Washington University Dispensary. All drugs are proportioned to body weight. The treatment consists of mercury with chalk by mouth, daily; weekly intramuscular injections of mercuric bichlorid (1 per cent. solution); and a bimonthly course of three injections of arsphenamin intravenously. An important feature of this method is that infants must continue such a routine at least one year, and older children at least two years, regardless of what the Wassermann reaction may be. The same treatment is continued longer if indicated by the Wassermann or the clinical signs. Arsphenamin therapy is preceded by examination of the cerebrospinal fluid, to prevent a Herxheimer reaction in the central nervous system. Intraspinal treatment (Swift-Ellis method) is resorted to in cases of infection of the central nervous system not responding to ordinary treatment.

186. Marshall, Mrs. B.: Report of Social Worker for Syphilitic Children. Washington University Dispensary and St. Louis Children's Hospital, December, 1920.

187. Engel and Türk: *Therap. Halbmonatsh.* **35**:242 (April 15) 1921.

188. Blechmann: *La Médecine* **2**:137 (Nov.) 1920.

189. Fordyce and Rosen: *J. A. M. A.* **75**:1385 (Nov. 20) 1920.

190. Jeans: *J. A. M. A.* **76**:167 (Jan. 15) 1921.

Findlay¹⁹¹ condemns the intramuscular administration of the arsenicals because of the likelihood of sloughing and necrosis. He adds that mothers always ask that arsphenamin and allied compounds be given intravenously. He advises against giving arsphenamin by way of the longitudinal sinus, on account of the dangers involved. "Neokharsivan" is the arsenical used by him. Fleming¹⁹² especially recommends the use of the scalp veins for intravenous therapy. He emphasizes the recognized fact that the younger the patient the greater is the likelihood of cure.

Morton Smith¹⁹³ denies the statement that arsphenamin has failed in the treatment of interstitial keratitis, and gives case reports to prove his point. In none of his cases was the eye condition aggravated by the arsphenamin. With regard to optic atrophy, Stokes¹⁹⁴ agrees with Ehrlich that arsphenamin is contraindicated in some cases of simple primary optic atrophy. He also agrees with Smith as to the excellent results obtained with arsphenamin in cases of keratitis. Stokes urges that deafness in hereditary or acquired syphilis should be treated no matter how long it lasts, for he has seen patients benefited occasionally. He corroborates Jeans' view that the expert seldom or never has need to use any other than the intravenous route for the administration of arsphenamin. The idea of the Welander homes for the treatment of cases of hereditary syphilis is strongly supported by Stokes. Jewesbury¹⁴ describes the course of treatment with novarsenobillon which he has used with success. Its effects on individual symptoms are noted. McKenna¹⁹⁵ has used virtually all the arsenicals including galyi. He now uses neokharsivan because of the infrequency of toxic reactions. In the discussion of McKenna's paper, Harrison said that neo-arsphenamin gave better therapeutic results than arsphenamin; but that neither could be given intramuscularly without causing a great deal of pain. On this account he welcomed sulfarsenol because it causes no more pain than the mercurials when given intramuscularly. Harrison urges continuation of treatment in cases with a persistently positive Wassermann reaction. He believes that under treatment the tissues "form the habit" of elaborating the substances discovered in the Wassermann reaction. According to Gralka,¹⁹⁶ who gives his results with 410 children, when the treatment is inadequate, a positive Wassermann may be obtained from fifteen to twenty years later.

191. Findlay: *Brit. M. J.* **2**:197 (Aug. 7) 1920.

192. Fleming: *Glasgow M. J.* **96**:257 (Nov.) 1921.

193. Smith: *Arch. Dermat. & Syph.* **4**:723 (Dec.) 1921.

194. Stokes: *Arch. Dermat. & Syph.* **4**:778 (Dec.) 1921.

195. McKenna: *Brit. M. J.* **2**:473 (Sept. 24) 1921.

196. Gralka: *Jahrb. f. Kinderh.* **92**:205, 1920.

THE ARSENICAL PREPARATIONS

Chemically identical substances are arsphenamin, arsenobillon, diarsenol (sodium arsphenamin), kharsivan; and neo-arsphenamin, novarsenobillon, neodiarsenol, neokharsivan.¹⁹⁷ Six different brands of arsphenamin studied by Voegtlin and Smith¹⁹⁸ were found to have approximately the same trypanocidal activity. Six different samples of neo-arsphenamin varied in this respect to a slightly greater extent. Schamberg¹⁹⁹ found that though the margin of safety is greater for neo-arsphenamin, arsphenamin itself has greater trypanocidal activity.

In order to secure greater uniformity of these products, the government²⁰⁰ issued tentative "specifications for arsphenamin," giving the required amount of protection for rats infected with *Treponema equiperdum*. There was virtually unanimity as to the advisability of some such assurance of uniformity, expressed by syphilographers consulted on the subject.

Opinion as to the relative merits of the different arsenicals seems still to be divided. Relative toxicity and relative trypanocidal and therapeutic activity (clinical and serologic), are, of course, the deciding criteria. Queyrat,²⁰¹ contrary to many French syphilographers, prefers arsphenamin to neo-arsphenamin, because of the greater rapidity with which a negative Wassermann reaction is obtained; because of the greater pain when some of the solution escapes into the tissues (a useful warning signal), and because of the greater incidence of hepatic reactions with neo-arsphenamin. In the experience of Michelson,²⁰² the two preparations have about the same action on lesions. He believes accurate comparison to be impossible, owing to individual reactions. Sodium arsphenamin (diarsenol) was found by Michelson and Siperstein²⁰³ to have the same degree of efficacy as the other arsphenamins. According to Wiesenach,²⁰⁴ tolerance for arsphenamin is increased threefold if injected in a 1 per cent. solution of sodium chlorid. An aqueous solution already alkalized, put up in ampoules under partial vacuum, is now among "new and non-official remedies."²⁰⁵

The search for some means of arsenical therapy other than that by the intravenous route is of interest to those treating hereditary syphilis,

197. Browning: Glasgow M. J. **96**:266 (Nov.) 1921.

198. Voegtlin and Smith: J. Pharmacol. & Exper. Therap. **16**:449 (Jan.) 1921.

199. Schamberg, Kolmer, and Raiziss: Am. J. M. Sc. **160**:25 (July) 1920. See also J. A. M. A. **75**:563 (Aug.) 1920, and *ibid.* **75**:766 (Sept. 11) 1920.

200. For full description of technic, see Am. J. M. Sc. **160**:25, 1920.

201. Quoted in Editorial, Med. Rec. **100**:597 (Oct. 1) 1921.

202. Michelson: J. A. M. A. **77**:399 (July 30) 1921.

203. Michelson and Siperstein: Arch. Dermat. & Syph. **4**:184 (Aug.) 1921.

204. Wiesenach: Berl. klin. Wchnschr. **5**:845 (July) 1921.

205. Solution Arsphenamin-Lowy, N. N. R., J. A. M. A. **76**:859 (March 26) 1921.

especially if they are unable or unwilling to master intravenous technic. Minet²⁰⁶ has encountered no persistent hardening nor prolonged pain resulting from small daily subcutaneous injections of neo-arsphenamin when given in 4.7 per cent. glucose to which a little phenol has been added.

The rectal administration of the arsphenamins is championed especially by Wright²⁰⁷ and by Mehrtens.²⁰⁸ According to the former, the blood vessels and lymphatics of the rectum and sigmoid convey most of the solution directly to the liver, whence it is distributed to the other tissues. The solution is given very slowly after starvation and enema. According to Wright, the indications for rectal administration are: (1) poor veins; (2) children; (3) hysterical and highly nervous patients. Findlay¹⁹¹ considers rectal administration of very doubtful value in children because of the fact that the liquid is frequently expelled very quickly.

Among numerous authors who vouch for the efficacy, painlessness and safety of intramuscular sulfarsenol,²⁰⁹ Dobie²¹⁰ maintains that this preparation is ideal for infants and for those with difficult veins.

"Silver arsphenamin" continues to receive favorable comment, especially from the German writers. In a review of the literature on this preparation, Michelson and Siperstein²¹¹ found forty-three German and three English articles. The drug is the sodium salt of silver-diaminodihydroxy-arseno-benzene;²¹² it contains 20 per cent. arsenic and 14 per cent silver. In view of the necessity for prolonged treatment in hereditary cases, it is of interest that, according to Michelson,²⁰² the therapeutic dose of silver arsphenamin is so small that it is better tolerated over long periods of time. It must be given intravenously,²¹³ as painful induration results when it is given intramuscularly. Several articles on the use of silver arsphenamin, most of them giving statistics favorable to the drug, have been published.²¹⁴

206. Minet: Bull. et mém. Soc. méd. d. hôp. de Par. **44**:1475 (Dec. 3) 1920.

207. Wright: New York M. J. **112**:275 (Aug. 28) 1920.

208. Mehrtens: J. A. M. A. **76**:574 (Feb. 26) 1921.

209. Crawford: Glasgow M. J. **96**:263 (Nov.) 1921. Pechère, in discussion of Findlay's paper, Brit. M. J. **2**:197 (Aug. 7) 1920. Tixier and Duval: Bull. et mém. Soc. méd. d. hôp. de Par. **45**:818 (June 3) 1921. Duroeux: Progrès méd. **36**:155 (April 9) 1921. Rawlins.¹⁸³

210. Doble: Lancet **2**:243 (July 31) 1920.

211. Michelson and Siperstein: Arch. Dermat. & Syph. **4**:193 (Aug.) 1921.

212. Fordyce: Arch. Dermat. & Syph. **4**:737 (Dec.) 1921.

213. Mengert: München. med. Wchnschr. **68**:13 (Jan. 7) 1921.

214. Naegeli: München. med. Wchnschr. **67**:1372 (Nov. 26) 1920. Zurhelle: Deutsch. med. Wchnschr. **46**:1354 (Dec. 2) 1920. Mouris: Siglo méd. **67**:937 (Dec. 11) 1920. Danyasz: Presse méd. **29**:74 (Jan. 26) 1921. Bering: Deutsch. med. Wchnschr. **46**:538 (May 13) 1920. Galewsky: München. med. Wchnschr. **67**:124 (Jan. 30) 1920. Hahn: Deutsch. med. Wchnschr. **46**:92 (Jan. 22) 1920. Scholz: Deutsch. med. Wchnschr. **46**:879, 1920. Parounagian: J. A. M. A. **77**:1706 (Nov. 26) 1921. Walson: Am. J. M. Sc. **161**:418 (March) 1921.

More recent work on the dosage and elimination of the arsenicals indicates that this form of antisyphilitic therapy can probably safely be made more intensive than has hitherto been customary. For example, the Pollitzer method of giving a daily dose of arsphenamin for three doses, followed by mercury injections, has been used without ill effect by both Ormsby²¹⁵ and Goodman.²¹⁶ Both report better and more rapid results in cases in which the usual method of treatment had failed.

Tollens²¹⁷ is most enthusiastic about the Linser method of treatment: i. e., intravenous injections of a neo-arsphenamin-mercuric chlorid mixture. He claims that this method has all the advantages and none of the drawbacks of the other plans of therapy. After two years' experience with a similar method, Zirn²¹⁸ also reports excellent results.

THE MERCURIAL PREPARATIONS

Wassermann⁵³ believes that mercury is effective mainly because it acts on the cells that have been changed by the poison of the disease, and also on the inversion of lipoid metabolism—thus constituting an antithesis to the arsenic preparations of Ehrlich, which exert a spirillicidal effect. The combined treatment with mercury and arsenic is thus thoroughly logical.

Klecan²¹⁹ believes that mercury can and should be given intravenously, and reports prompt symptomatic and serologic results. The salt preferred by Lane²²⁰ for intravenous use is mercury cyanid. His routine is one injection of an arsphenamin substitute and five injections of the cyandid solution per week. Phlebitis occurred in two cases out of 5,000.

Valuable studies on the relative efficiency of the different mercurial preparations in the treatment of hereditary syphilis, are those of Ramsey and Groebner.²²¹ By quantitative analysis of the elimination of mercury in the urine, they came to the following conclusions: 50 per cent. ointment is to be preferred to the less concentrated forms, and need not be repeated oftener than twice weekly. The quantity absorbed is much increased by friction. Calomel ointment is absorbed less rapidly and to a less extent, and should, therefore, be given in greater concentration. Mercury salicylate in oil should be given hypodermically twice weekly instead of once. Mercuric chlorid, by hypodermic injections, although the dose is very small, continues to be eliminated for six or seven days.

215. Ormsby: J. A. M. A. **75**:1 (July 3) 1920.

216. Goodman: New York M. J. **112**:494 (Oct. 2) 1920.

217. Tollens: Therap. Halbmonatsh. **35**:212 (April 1) 1921.

218. Zirn: München. med Wchnschr. **67**:1017, 1920.

219. Klecan: Northwest Med. **19**:266, 1920.

220. Lane, J. E.: Lancet **2**:796 (Oct. 15) 1921.

221. Ramsay and Groebner: Am. J. Dis. Child. **20**:199 (Sept.) 1920.

The authors found bichlorid therapy frequently followed by the appearance of protein in the urine, and consider that on that account it should be excluded from the treatment of syphilis in children. Advocates of bichlorid therapy do not admit the validity of this objection. Calomel by mouth is absorbed in small amounts, and continues to be eliminated for a considerable time, so that it is probable that it would be sufficient to give it at intervals of several days, thus avoiding diarrhea. Gray powder is absorbed to a small degree and eliminated rather rapidly, so that large doses, repeated daily, would probably be necessary to maintain mercury in the circulation.

Cole and his associates,²²² studying mercury inunctions, concluded that the only mercury absorbed is that part which is rubbed into the hair follicles and entrances of the sebaceous and sweat glands. Hence all superfluous ointment may be cleansed off immediately after the inunction without lessening the effect. A study of insoluble mercury injections by means of the roentgen ray²²³ led to the conclusion that even after four months much of the mercury of gray oil may remain unabsorbed, and that the occasional increase in speed of absorption is capable of producing dangerous cumulative effects.

Hirschberg²²⁴ considers the mercurials indispensable in the treatment of certain gummatous affections of the eye in hereditary syphilis. A special preparation—novasurol—which contains 39 per cent. mercury has been found very effective when given in conjunction with neosarsphenamin.²²⁵ Engel and Türk¹⁸⁷ also vouch for this preparation.

TREATMENT OF NEUROSYPHILIS

There has been much to substantiate, and apparently nothing to disprove, the assertion of Fordyce¹¹³ that the spirochete invades the central nervous system, if at all, during the early general dissemination. Obviously, this is the time for intensive treatment, if neurosyphilis is to be prevented. In all probability the central nervous system in hereditary cases is infected during intrauterine life; so that the only really satisfactory prophylaxis against such a complication is the general one already discussed: treatment of the mother before or during pregnancy. It is, however, safe to say that the earlier treatment is begun and spinal puncture performed in any case of heredosyphilis the less will be the likelihood of development of neurosyphilis. An event which no doubt occurs in hereditary cases (though there have been no reports to that effect) as it has in acquired²²⁶ cases is the development of neurosyphilis

222. Cole, Gericke, and Sollmann: *J. A. M. A.* **77**:2022 (Dec. 24) 1921.

223. Cole, Littmann, and Sollmann: *J. A. M. A.* **75**:1559 (Dec. 4) 1920.

224. Hirschberg: *Deutsch. med. Wchnschr.* **46**:1382 (Dec. 9) 1920.

225. Bruck and Becher: *München. med. Wchnschr.* **67**:901, 1920.

226. Lakaye: *Arch. méd. Belge.* **73**:587 (July) 1920; abstr. *J. A. M. A.* **76**:70 (Jan. 1) 1920.

shortly after thorough treatment with arsphenamin. Moore,²²⁷ however, found that in treated cases, 12.7 per cent. of spinal fluids were positive, as against 25 per cent. in untreated cases. Undoubtedly some such reduction in neurosyphilis can be effected among heredosyphilitics, though treatment must be begun too late in many cases.

Among others, Guy²²⁸ prefers to exhaust intensive general anti-syphilitic medication before resorting to intraspinal therapy. Some observers, however, believe that the earlier intraspinal therapy is begun, the greater will be the likelihood of cure of neurosyphilis. Dercum²²⁹ is a strong supporter of "spinal drainage" in the treatment of neurosyphilis. He considers that the withdrawal of spinal fluid during general antisymphilitic treatment is itself a valuable procedure. Stokes and Osborne,²³⁰ comparing cases not receiving spinal drainage with those receiving it, obtained no evidence favoring the drainage method. In both groups, a transient but marked rise in the cell count, followed by a fall, occurred frequently. In their experience, the Swift-Ellis-Ogilvie method of intraspinal treatment (already reviewed by Jeans¹) produced more satisfactory and gave more permanent results.

Hüsgen²³¹ says that it is well recognized that nerve tissue absorbs very little mercury, mentioning Serono's attempt to produce a lipotropic mercury compound in cholesterin mercury oleate. The compound studied by Hüsgen was one containing mercury, acetanilid and toluol ("M-A-T"). Though slowly absorbed, it was found in relatively high content in nerve tissue. Its effect on neurosyphilis is not mentioned.

The experimental and clinical investigations of Lafora²³² have convinced him that substances injected intraspinally soon rise to the brain, and that intraspinal therapy is of great benefit in neurosyphilitic processes which have not yet involved the parenchyma. Samovici²³³ says that Marinesco has used the arsphenaminized serum technic for ten years, and that he has obtained maximum improvement in incipient syphilitic paraplegia, 50 per cent. improvement in the mania and melancholia forms of general paresis, and virtually no improvement in tabes. Mitchell²³⁴ testifies to the safety and therapeutic value of the Swift-Ellis treatment. Keidel and Moore²³⁵ deny the assertion that the efficacy of intraspinal therapy depends on increased permeability of the meninges, adding that aseptic meningitis produced by irritants may

227. Moore: J. A. M. A. **76**:769 (March 19) 1921.

228. Guy: Arch. Dermat. & Syph. **2**:53 (July) 1920.

229. Dercum: Arch. Neurol. & Psychiat. **3**:230 (March 20) 1920.

230. Stokes and Osborne: J. A. M. A. **76**:708 (March 12) 1921.

231. Hüsgen: Biochem. Ztschr. **112**:1 (Nov.) 1920.

232. Lafora: Rev. neurol. **26**:625 (Aug.) 1919.

233. Samovici: Rév. méd. d. Rosario **11**:138 (July) 1921; abstr. J. A. M. A. **77**:1375 (Oct. 22) 1921.

234. Mitchell: Arch. Dermat. & Syph. **2**:44 (July) 1920.

235. Keidel and Moore: Bull. Johns Hopkins Hosp. **31**:404 (Nov.) 1920.

prove to be an untoward rather than a beneficial factor. Mehrtens²³⁶ warns against any routine system of intraspinal therapy, insisting that each case be treated according to individual requirements.

Excellent results are claimed²³⁷ for intraspinal injections of a hypertonic solution of a minute dose of neo-arsphenamin mixed with the patient's own spinal fluid. In a comprehensive review of intraspinal therapy, Boudreau²³⁸ gives precedence to the Swift-Ellis-Ogilvie method, adding that the mercurialized serum method of Byrnes is more dangerous and produces more severe reactions. He considers that the drainage method of Dercum is not without danger, is extremely painful, and that the results obtained are not in agreement. Sicard²³⁹ claims excellent results in neurosyphilis, with small doses of neo-arsphenamin intravenously, given every day or two.

A study of the nonspecific treatment of neurosyphilis has been made by Mühlens and his associates.²⁴⁰ It was found that the injection of malarial parasites, or of the spirilla of relapsing fever, produced a favorable effect on the syphilitic infection. Whether this was due to hyperthermia alone or to an immunity reaction was not determined.

Lafora²⁴¹ declares that no authentic instance of a permanent cure of paresis or of tabes has ever been published, although the long remissions and periods of improvement often simulate a cure. Contrary to the opinion of Keidel and Moore,²³⁵ Lafora ascribes the benefit from intraspinal therapy to the reactional process in the meninges, which renders the plexus more permeable to drugs given by the vein.

When to consider that a case of syphilis, particularly neurosyphilis, hereditary or otherwise, has been cured, is a question still under discussion. Capurro²⁴² cites the opinion of Vernes, that if the spinal fluid is normal after provocative injection of an arsenical, and if the negative reaction of the fluid persists for eight months, examinations being made monthly, either the subject never had syphilis, or has completely recovered. Capurro's ten years' experience has produced nothing to conflict with Vernes' findings.

Jacobi,²⁴ it will be remembered, has denied that reinfection with syphilis is evidence that the disease has been cured. Similarly,

236. Mehrtens: *Colorado M. J.* **18**:385 (Nov.) 1920.

237. Ravaut, Arbeit, and Rabeau: *Paris méd.* **10**:353 (Nov. 13) 1920; abstr. *J. A. M. A.* **76**:71 (Jan. 1) 1921.

238. Boudreau: *Med. Rec.* **100**:555 (Sept. 24) 1921.

239. Sicard: *Presse méd.* **28**:281 (May 8) 1920; abstr. *J. A. M. A.* **75**:66 (July 3) 1920.

240. Mühlens, Weygandt, and Kirschbaum: *München. med. Wchnschr.* **67**:831, 1920.

241. Lafora: *Siglo méd.* **68**:624 (June 25) 1921; abstr. *J. A. M. A.* **77**:1375 (Oct. 22) 1921.

242. Capurro: *Anal. de la fac. de méd., Montevideo* **5**:562 (Sept.-Oct. 1920; abstr. *J. A. M. A.* **76**:826 (March 19) 1921.

Goubeau²⁴³ states that a heredosyphilitic may contract the disease *de novo*, and that it may follow the ordinary course of acquired syphilis. The author is satisfied that the spirochetes still persist in the tissues, but that through a process of adaptation they have become inactive. Fresh spirochetes from without may now prove infectious, and may even add to the gravity of the case. Thus we must accept the idea of superinfection, or, as the author calls it, hypersyphilis. Evidence of the opposite character exists, showing that some heredosyphilitics are wholly, while others are partly immunized.

REACTIONS FOLLOWING TREATMENT

1. *Distribution and Elimination of Arsphenamin and Its Allies.*—Obviously, the method and rate of elimination have much to do with the nature and degree of reaction. Pomaret²⁴⁴ found that most of the arsphenamin injected intravenously is eliminated very rapidly—much less so by the kidneys than by the intestines (especially through the bile). A very small fraction is eliminated slowly. Simultaneous mercurial treatment retards elimination. These observations have been substantiated by the experimental work of Jeans and Clausen,²⁴⁵ who found that following an intravenous dosage of 10 mg. per kg. of body weight, 90 per cent. of the arsenic had left the circulation within half an hour. The corpuscles were nearly arsenic free. Penetration of arsenic into the spinal fluid is greatest in cases with evidences of meningeal irritation, and diminishes with the age of the patient, and with each succeeding injection of arsphenamin. After the injection of arsphenamin in kittens, the liver and intestines show the highest arsenic content. Arsenic is practically absent from the brain, skin and muscles. In human subjects five times as much arsenic leaves the body in stools as in urine. The excretion can be detected for two or three weeks. Even at this time, about 50 per cent. of the arsenic remains in the body.

2. *Factors Relating to the Technic.*—There seems to be no question that shaking alkalized solutions of arsphenamin and neo-arsphenamin in the presence of air greatly increases the toxicity.²⁴⁶ Preparations of neo-arsphenamin which have become difficultly soluble are usually highly toxic even without shaking. The Cologne Arsphenamin Commission²⁴⁷ concluded that though fatalities are extremely rare in arsphenamin therapy, dosage in excess of the recognized limits of safety plays a very important part in their production. In all cases of dermatitis, and in six out of ten cases of encephalitis, overdosage was

243. Goubeau: Bull. Soc. franç. de dermat. et syph. No. 3, 1920; abstr. Am. J. Syphilis 5:140 (Jan.) 1921.

244. Pomaret: La Médecine 2:123 (Nov.) 1920.

245. Jeans and Clausen: Missouri M. J. 19:43 (Jan.) 1922.

246. Pub. Health Rep. 35:2205 (Sept. 17) 1920.

247. Deutsch. med. Wchnschr. 46:299 (March 11) 1920.

shown to be responsible. This commission confirmed the observation that a timid administration or too short courses of treatment may favor the reappearance of central nervous symptoms.

The importance of slow administration of the arsenicals is emphasized by Roth,²⁴⁸ who found that rapid administration enormously increased toxicity.

Hunt²⁴⁹ found that not only shaking, but also warming the solution, or allowing it to stand in air, increased the toxicity. Preparing and injecting solutions at low temperature produced no change, though cold may preserve toxicity already present.

3. *Factors Relating to the Drug.*—From the fact that the percentage of reactions is as great in nonsyphilitics as in syphilitics, and from other experimental studies, Strickler²⁵⁰ concludes that the drug is more likely to be responsible for reactions than the patient. He attributes the majority of reactions to some impurity in the arsphenamin, or to some chemical reaction between the arsphenamin and the chemical constituents of the patient's blood, or to both.

Raiziss and Proskouriakoff²⁵¹ state that the impurity causing reactions is present only in very small quantity. In a chemical study of the toxicology of neo-arsphenamin, Raiziss and Falkov²⁵² found that variation in the completeness of substitution in the amino groups (variation in the arsenic-to-nitrogen ratio) accounts for the irregularity of the toxicity and therapeutic effect of neo-arsphenamin. Queyrat²⁵³ urges that manufacturers should be obliged to state on the label the content of the toxic substance—amino-oxyphenyl-arsenoxid. To cite a single example of the importance of such studies, we may mention Cheinisse's report²⁵⁴ of four crises bordering on asphyxia, in patients given a certain lot of novarsenobenzol, who had previously been given the same drug in large doses without ill effect. Cheinisse quotes Billon's remark that of two samples of the same preparation, the chemist will say one is toxic, and the physiologist the other. Unfortunately, the patient, rather than the rabbit, must often be the test animal.

Contrary to some observers, Pomaret²⁵⁵ does not believe that arsenoxid is responsible for the symptoms of shock ("nitritoid crisis"), produced by some arsenicals, for he found that arsenoxid raises the

248. Roth: Arch. Dermat. & Syph. **2**:292 (Sept.) 1920.

249. Hunt, R.: J. A. M. A. **76**:854 (March 26) 1921.

250. Strickler: Arch. Dermat. & Syph. **2**:692 (Dec.) 1920.

251. Raiziss and Proskouriakoff: Arch. Dermat. & Syph. **2**:280 (Sept.) 1920.

252. Raiziss and Falkov: J. Biol. Chem. **46**:209 (Mar.) 1921.

253. Queyrat: Bull. et mém. Soc. méd. d. hôp. de Par. **45**:446 (April 8) 1921.

254. Cheinisse: Presse méd. **29**:386 (May 14) 1921.

255. Pomaret: Bull. méd., Par. **35**:743 (Sept. 17) 1921.

blood pressure of dogs. In such crises the blood pressure is lowered. Hunt²⁴⁹ found that this substance is formed when arsphenamin solutions are shaken, warmed, or allowed to stand, and attributes to it the toxic symptoms following such procedures. His observations strongly support the idea that the physical condition (colloidal?) of the solution, or the presence of a very labile toxic compound may, at times, account for untoward reactions.

4. *Factors Relating to the Patient.*—Kolmer and Lucke²⁵⁶ found that the tissue changes produced by neo-arsphenamin are of the same character as those produced by arsphenamin, but less severe in proportion to the dosage. Tokuda²⁵⁷ strongly opposes Berman's theory (reviewed by Jeans¹) attributing untoward reactions to precipitation of serum globulins. He has confirmed the relative increase in globulins, but he attributes untoward reactions either to technical errors in administration or to the presence of impurities in the drug.

The phenomenon of rise in pulmonary pressure following arsphenamin injections has been studied by M. I. Smith²⁵⁸ and by Jackson and Rapp.²⁵⁹ The former believes the phenomenon to be due to the mechanical blocking or constricting action of the pulmonary vessels, depending on the amount of alkali used. According to Jackson and Rapp, first class preparations of arsphenamin have no direct action on the bronchial musculature of dogs.

HEPATIC REACTIONS

It has been found²⁶⁰ that when the liver is damaged by arsphenamin increase in the cholesterol content of the blood is early and marked—a valuable sign of a precarious liver condition in patients under treatment. On account of the high blood urea values frequently found in patients with hepatic reactions, a diet rich in nitrogen is condemned, as is also too free exercise. The suggestion that arsphenamin produces jaundice by rendering the liver more liable to bacterial invasion, has been fairly well discredited by studies in agglutination (Walker) and pathology (Turnbull²⁶¹). It seems far more likely that the effect is direct rather than indirect.

Brocq²⁶² gives convincing evidence of the dual effect on hepatic tissue of the spirochetes, on the one hand, and of the arsenical spirocheticide, on the other. Cases in which toxic injury of the liver

256. Kolmer and Lucke: *Arch. Dermat. & Syph.* **2**:289 (Sept.) 1920.

257. Tokuda: *Arch. Dermat. & Syph.* **4**:512 (Oct.) 1921.

258. Smith, M. I.: *J. Pharmacol. & Exper. Therap.* **15**:279 (June) 1920.

259. Jackson and Rapp: *J. Lab. & Clin. M.* **6**:1 (Oct.) 1920.

260. Editorial, *J. A. M. A.* **75**:543 (Aug. 21) 1920.

261. London Letter, *J. A. M. A.* **76**:189 (Jan. 15) 1921.

262. Brocq: *Bull. méd., Par.* **35**:235 (March 19) 1921.

reduces its resistance, thus enabling the spirochetes to damage it further, require the continued administration of arsphenamin. Cases in which toxic injury by the drug is the sole factor, naturally require immediate cessation of arsenotherapy. Katsainos²⁶³ cites Ravaut²⁶⁴ as showing that when the liver is damaged, its proteopexic ability is abolished, and, albuminous substances passing through unchanged, produce hemolysis in the general circulation. This is caused by many diseases, mostly febrile, and by different chemicals, including arsphenamin. In a recent article, Milian²⁶⁵ restates his opinion (reviewed by Jeans¹) that the icterus is due to the syphilitic infection, and that treatment should be continued, or if it has been discontinued it should be begun again.

Interesting case reports of hepatic reactions, with necropsy findings in some of the fatal cases, are given by Foulerton,²⁶⁶ Silbergleit and Föckler,²⁶⁷ and Todd.²⁶⁸ The relative frequency of such reactions in the winter months is noted in the two articles last named.

CUTANEOUS REACTIONS

Moore and Keidel²⁶⁹ report twenty-three cases of the dermatitis group of reactions. Of the eighteen severe reactions, five were fatal (27.7 per cent.). The authors believe that the reactions were anaphylactic in origin. Three cases of dermatitis of the lichen ruber type are reported.²⁷⁰ Discussions and case reports of dermatitis exfoliativa following arsenotherapy have been presented by several authors (Whiteside,²⁷¹ French,²⁷² Stuart and Maynard²⁷³).

The strong probability of the anaphylactic nature of such reactions calls to mind the suggestion²⁷⁴ that drug reactions may depend on the formation of compounds between the drug and the body proteins, so that what amount to foreign proteins are formed. It is also noteworthy that Auer²⁷⁵ has demonstrated that anaphylactic reactions may be caused in the skin by substances which themselves do not

263. Katsainos: J. A. M. A. **76**:195 (Jan. 15) 1921.

264. Ravaut: Presse méd. **28**:893 (Dec. 11) 1920.

265. Milian: La Médecine **2**:113 (Nov.) 1920.

266. Foulerton: Brit. M. J. **1**:864 (June 26) 1920.

267. Silbergleit and Föckler: Ztschr. f. klin. Med. **88**:333, 1919; abstr. J. A. M. A. **75**:1300 (Nov. 6) 1920.

268. Todd: Lancet **1**:632 (March 26) 1921.

269. Moore and Keidel: Arch. Int. Med. **27**:716 (June 15) 1921.

270. Buschke and Freymann: Med. Klin. **17**:899 (July 24) 1921; abstr. J. A. M. A. **77**:1215 (Oct. 8) 1921.

271. Whiteside: Northwest Med. **20**:153 (June) 1921.

272. French: Lancet **1**:1262 (June 12) 1920.

273. Stuart and Maynard: Arch. Int. Med. **26**:511 (Nov. 15) 1920.

274. Editorial, J. A. M. A. **75**:1070 (Oct. 16) 1920.

275. Auer: J. Exper. Med. **32**:427 (Oct.) 1920.

produce anaphylaxis. Stuart and Maynard,²⁷³ in reporting their case, noted that cutaneous hypersensitiveness to arsphenamin and neoarsphenamin occurs in patients who have suffered from exfoliative dermatitis. Strickler²⁷⁶ showed that arsphenamin given intravenously can stimulate the production of a luetin test in nonsyphilitic patients, as well as a positive Pirquet test, previously negative. Cutaneous tests for food sensitization were not affected by arsphenamin.

With regard to silver arsphenamin, Stühmer²⁷⁷ reports the occurrence of numerous cases of dermatitis following the use of the drug; and Lochte²⁷⁸ reports a case of argyria.

REACTIONS REFERABLE TO THE CENTRAL NERVOUS SYSTEM

Though Herxheimer (focal) reactions to arsenotherapy may occur anywhere, as in the liver or intestine,²⁷⁹ it is in the central nervous system that such reactions are most likely to be dangerous. Such focal reactions are given diagnostic value by Speroni,²⁸⁰ who considers them analogous to focal reactions to tuberculin in cases of tuberculosis.

Epileptiform seizures²⁸¹ and neuroretinitis²⁸² have also been reported—plausible reasons being given in each case for considering the therapy responsible, rather than the disease itself.

With regard to reactions to intraspinal treatment, fever, nausea, vomiting and pains following shortly after injections, occur so frequently that relatively little consideration is given them. In most cases, the advantages of the treatment far outweigh such disadvantages. Occasionally, however, more severe reactions are noted. In one case,²⁸³ complete paralysis of the legs, with incontinence of urine and feces, followed the fourth intraspinal injection. The paralysis improved. Jacobi²⁸⁴ reports two fatalities following endolumbar injection of sodium arsphenamin by Gennerich's technic. Necropsy showed severe irritation, with hemorrhages in the pia. In one case of cerebrospinal syphilis treated intraspinally by Keidel and Moore,²⁸⁵ the first injection

276. Strickler: *Arch. Dermat. & Syph.* 4:177 (Aug.) 1921.

277. Stühmer: *München, med. Wchnschr.* 67:836, 1920.

278. Lochte: *Therap. Halbmonatsh.* 34:334 (June 15) 1920; abstr. *J. A. M. A.* 75:1168 (Oct. 23) 1920.

279. Herxheimer: *Berl. klin. Wchnschr.* 57:369, 1920.

280. Speroni: *Sémana méd.* 28:725 (June 23) 1921; abstr. *J. A. M. A.* 77:1057 (Sept. 24) 1921.

281. Bejarano: *Siglo méd.* 67:302 (April 24) 1920; abstr. *J. A. M. A.* 75:278 (July 24) 1920.

282. Oden and White: *Am. J. Ophth.* 4:365 (May) 1921.

283. Aldabalde: *Siglo méd.* 68:285 (March 19) 1921; abstr. *J. A. M. A.* 76:1619 (June 4) 1921.

284. Jacobi, W.: *Therap. Halbmonatsh.* 35:307 (May 15) 1921; abstr. *J. A. M. A.* 77:1059 (Sept. 24) 1921.

285. Keidel and Moore: *Am. J. M. Sc.* 162:209 (Aug.) 1921.

was thought to have set up an aseptic meningitis, with partial occlusion of one or more foramina of exit from the fourth ventricle, and resulting internal hydrocephalus. This danger from intraspinal therapy is characterized as "possible though remote."

MISCELLANEOUS REACTIONS

Among the miscellaneous reactions reported are (1) two cases of aplastic anemia (in women);²⁸⁶ (2) a case of stomatitis with aplastic anemia (fatal) which the authors²⁸⁷ considered related to the dermatitis exfoliativa type of reaction; (3) a case of hemorrhagic purpura²⁸⁸ which was considered to be similar in nature to the cases of epileptiform convulsions following injections, in which post mortem examination shows punctate hemorrhages in the brain, attributable to damage of capillary epithelium by the remedy. Lesne²⁸⁹ reports a case in which the fourth dose of neo-arsphenamin (following three well tolerated doses) was followed by anuria and acute uremia, with death on the eighth day. A case with nitritoid crises accompanied by transient myopia and albuminuria is reported by Milian and Périn.²⁹⁰

According to Gougerot,²⁹¹ the causes of late reactions to the arsenicals are (1) arsenical lesions of the viscera, (2) recurrence of "unextinguished" syphilis, (3) "tertiarization," i. e., increase in destructive tendency of the lesions.

REACTIONS TO MERCURY

Such common reactions as salivation, diarrhea, renal damage, etc., have been discussed fully and allowance has been made for them in the various plans of treatment. Klauder and Kolmer⁷¹ cite clinical and experimental observations to show that mercury is considerably more nephrotropic than arsphenamin or neo-arsphenamin. In intensive treatment with both mercury and the arsenicals, the nephrotropic action of mercury may retard the elimination of arsenic, and in this way cause untoward effects of arsenic (an opinion concurred in by Pomaret²⁴⁴). Such conjoined intensive treatment is, therefore, not advised. Two fatal cases of stomatitis due to mercury are reported.²⁹² One patient died following involvement of the facial bones. The other had extensive necrosis of the mandible.

286. Gorke: München. med. Wchnschr. **67**:1226 (Oct. 22) 1920.

287. Moore and Keidel: Arch. Dermat. & Syph. **4**:169 (Aug.) 1921.

288. Anwyll-Davies: Brit. J. Dermat. & Syph. **33**:264 (July) 1921.

289. Lesne: Bull. et mém. Soc. méd. d. hôp. de Par. **45**:399 (March 18) 1921; abstr. J. A. M. A. **76**:2433 (May 21) 1921.

290. Milian and Périn: Paris méd. **11**:388 (Nov. 12) 1921.

291. Gougerot: La Médecine **2**:119 (Nov.) 1920.

292. Gérard-Maurel and Rénard: Rev. de stomatol. **22**:12 (Dec.) 1920.

PREVENTION AND TREATMENT OF REACTIONS TO ARSENOTHERAPY

The foregoing consideration of toxicology and of toxic reactions naturally contains many implicit suggestions for the prevention of such reactions. Certain additional observations should be mentioned, as having a more direct bearing upon the prophylaxis and treatment of these conditions. Working with mice, Kolle²⁹³ found that a small intravenous dose of arsphenamin furnished perfect protection against a fatal dose of the same drug injected twenty-four hours later. This furnishes an experimental basis for the clinical custom of giving small doses at the start of a course of treatment. Lake²⁹⁴ notes a definite decrease in toxicity if alkali is added up to 30 per cent. in excess of the amount necessary to form the disodium salt of arsphenamin. Neutralization as ordinarily carried out goes to a point midway between the monosodium and the disodium salts.

Busman²⁹⁵ studied cases of repeated acute reactions, usually considered personal idiosyncrasies to the drug. The observation of Stokes that atropin and induced anaphylaxis are of value in treating the condition, was confirmed by the author. Both dividing the dose and preceding it by atropin are of greater value than either method alone, and may be the means of permitting patients to take the drug who might otherwise be deprived of it. Sicard²⁹⁶ advises limiting the shock reaction to one limb by applying a constricting band to the root of the limb into which the injection is made, slowly removing this five minutes later. Two patients constantly presenting severe nitritoid crises after every injection of neo-arsphenamin, were tided past the danger point by this simple method. The procedure is called "arsenical anticlasis by topophylaxis." There was never any sign of local flocculation or precipitation in these cases.

Cheinisse²⁹⁷ strongly recommends Sicard's preliminary injection of 30 c.c. of physiologic solution of sodium chlorid containing 0.6 or 0.75 gm. sodium carbonate. The arsenical is injected through the same needle. Even after the appearance of arsphenamin shock, the immediate injection of 10 c.c. of a 10 per cent. solution of sodium carbonate may abort it. Other methods considered are: addition of 3 or 4 drops of ether to the arsenical (Kopaczewski); dissolving the arsenical in 20 per cent. solution of saccharose; injecting 3 c.c. of ether subcutaneously ten minutes before the arsenical; injecting 5 c.c. camphorated

293. Kolle: *Med. Klin.* **16**:355 (April 4) 1920.

294. Lake: *Am. J. Syphilis* **5**:96 (Jan.) 1921.

295. Busman: *J. A. M. A.* **76**:1302, 1921.

296. Sicard, Paraf, and Forestier: *Bull. et mém. Soc. méd. de hôp. de Par.* **45**:775 (May 27) 1921.

297. Cheinisse: *Presse méd.* **29**:506 (June 25) 1921.

oil half an hour before it. Sicard and Paraf²⁹⁸ consider that sodium carbonate is of value as preventing flocculation. Milian, discussing their paper, said that he uses sodium hydroxid in much the same way, but believes that it acts by preventing the splitting up of the arsenical, which is responsible for the nitritoid crises in connection with supra-renal insufficiency. Queyrat²⁵³ urges, in case of mishap, prompt venesection, and instillation, by the drip method, of 1,000, or 1,500 c.c. physiologic solution of sodium chlorid with glucose. He also advises that epinephrin be given daily, up to 5 or 6 mg. Lumbar puncture is also required, but the main indication is to give mercurial treatment to check the action of the disease on the nervous centers. Gastou²⁹⁹ advises that the urine be examined before every injection, especially for the presence of albumin and bile pigments. He adds that a solution of epinephrin should always be at hand.

The conclusion of Strickler,³⁰⁰ that neither atropin nor epinephrin prior to arsphenamin injections has any influence on early reactions, is of considerable interest.

Two fatal cases of cerebral reaction reported by Hitch,³⁰¹ in which widespread capillary hemorrhages were found, lend support to Dudley's theory that anoxemia caused by interalveolar hemorrhage has much to do with reactions. On this account, the continuous administration of oxygen is urged as the only hope in such cases. Ross³⁰² is an advocate of preliminary administration of atropin.

To obviate the annoying "lumbar puncture headaches," Baar³⁰³ gives salt solution intravenously, following each lumbar puncture. In a series of fifty punctures, only three headaches followed the use of this method.

298. Sicard and Paraf: *Bull. et mém. Soc. méd. d. hôp. de Par.* **45**:11 (Jan. 14) 1921; abstr. *J. A. M. A.* **76**:897 (March 26) 1921.

299. Gastou: *Bull. med., Par.* **34**:954 (Oct. 30) 1920; abstr. *J. A. M. A.* **76**:71 (Jan. 1) 1921.

300. Strickler: *New York M. J.* **112**:498 (Oct. 2) 1920.

301. Hitch: *Lancet* **1**:1311 (Jan. 19) 1920.

302. Ross: *Northwest Med.* **21**:63 (March) 1921.

303. Baar: *Med. Rec.* **98**:598 (Oct. 9) 1920.

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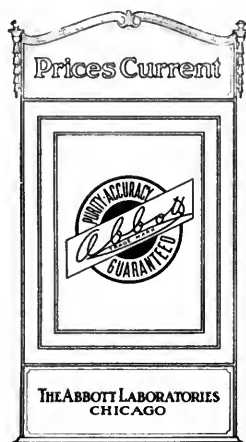
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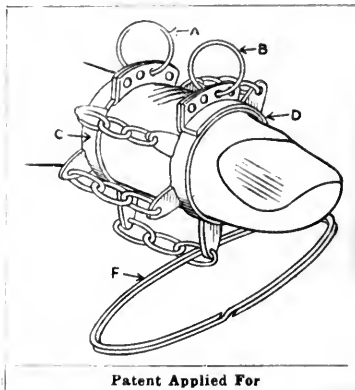


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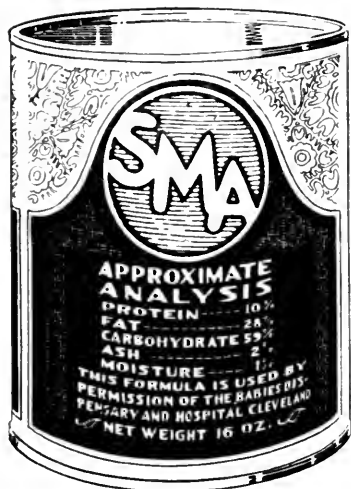
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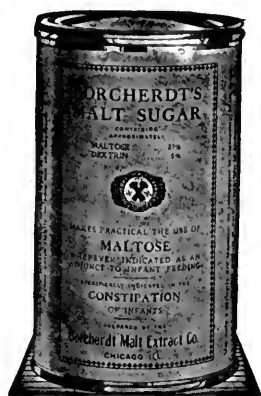
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